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(54) **SOLID DISPERSIONS COMPRISING TACROLIMUS**

TACROLIMUS ENTHALTENDE FESTE DISPERSIONEN

DISPERSIONS SOLIDES COMPRENANT DU TACROLIMUS

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The file contains technical information submitted after the application was filed and not included in this specification

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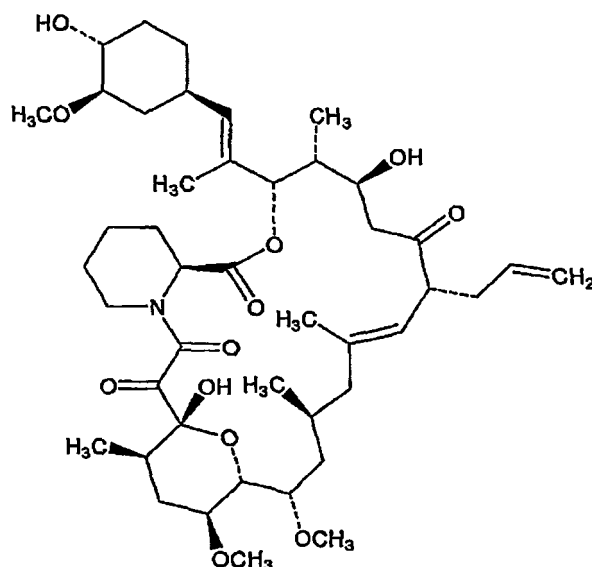
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Description

[0001] The present invention relates to a solid solution comprising tacrolimus having enhanced bioavailability, more specifically a solid solution of tacrolimus in a hydrophilic vehicle; a pharmaceutical composition comprising the solid solution, and dosage forms comprising the solid solution.

BACKGROUND OF THE INVENTION

[0002] Tacrolimus, also known as FK-506 or FR-900506, has the chemical tricyclic structure shown below:



corresponding to $C_{44}H_{69}NO_{12}$. Tacrolimus appears in the form of white crystals or crystalline powder. It is practically insoluble in water, freely soluble in ethanol and very soluble in methanol and chloroform.

[0003] The preparation of tacrolimus is described in EP-A-0 184 162 and analogues of tacrolimus are disclosed e.g. in EP-A-0 444 659 and US 6,387,918.

[0004] Tacrolimus is a macrolide compound with useful immunosuppressive activity, antimicrobial activity and other pharmacological activities and is of value for the treatment or prevention of rejection reactions by transplantation of organs or tissues, graft versus host diseases, autoimmune diseases and infectious diseases. Tacrolimus prolongs the survival of the host and transplanted graft in animal transplant models of liver, kidney, heart, bone marrow and small bowel and pancreas, lung and trachea, skin, cornea and limb.

[0005] In animals, tacrolimus has been demonstrated to suppress some humoral immunity and, to a greater extent, cell-mediated reactions such as allograft rejection, delayed type hypersensitivity, collagen-induced arthritis, experimental allergic encephalomyelitis and graft-versus-host disease.

[0006] Tacrolimus inhibits T-lymphocyte activation, although the exact mechanism of action is unknown. Experimental evidence suggest that tacrolimus binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed and the phosphatase activity of calcineurin inhibited. This effect may prevent the dephosphorylation and translocation of nuclear factor of activated T-cells, a nuclear component thought to initiate gene transcription for the formation of lymphokines. The net result is the inhibition of T-lymphocyte activation, i.e. immunosuppression.

[0007] Tacrolimus is extensively metabolized by the CYP3A4 isoenzyme in the gut wall and liver. Therefore, drugs that affect this isoenzyme may influence absorption and the subsequent elimination of systemically absorbed tacrolimus. Inhibitors of CYP3A4 may increase tacrolimus levels, while inducers of CYP3A4 may increase the metabolism of tacrolimus and decrease tacrolimus levels. Accordingly, tacrolimus may be administered together with one or more CYP3A4 inhibitors in order to improve the overall bioavailability.

[0008] Usually tacrolimus is administered orally and is therefore absorbed from the gastrointestinal tract. It has been observed that the absorption is negatively influenced by the simultaneous ingestion of food. Thus, the rate and extent of tacrolimus absorption were greatest under fasted conditions.

[0009] In general, it is known that the absorption and bioavailability of a therapeutically active substance can be

affected by a variety of factors when administered orally. Such factors include the presence of food in the gastrointestinal tract and, in general, the gastric residence time of a drug substance is significantly longer in the presence of food than in the fasted state. If the bioavailability of a drug substance is affected beyond a certain point due to the presence of food in the gastrointestinal tract, the drug substance is said to exhibit a food effect. Food effects are important because absorption and hence the plasma levels becomes highly variable depending on food intake. Absorption into the blood-stream may be adversely affected to the point that the patient risks insufficient absorption to remedy the condition for which the drug was administered. On the other hand, the very high peak concentrations seen at fasted conditions occasionally, may very well induce significant side effects, of nephro- or neuro-toxic origin, as well as GI side-effects and others.

[0010] Absorption of tacrolimus from the gastrointestinal tract after oral administration is rapid with a mean time-to-peak concentration (t_{max}) of approximately 1-2 hours after administration to healthy subjects or kidney or liver transplanted patients, but incomplete and variable. The bioavailability is generally as low as at the most about 20% after oral administration.

[0011] Frequently observed side effects are vomiting and nausea but side effects like tremor, headache, hypertension, renal dysfunction, hyperkalemia, hypomagnesaemia, hyperglycemia, insomnia, diarrhea, constipation, abdominal pain, nephrotoxicity and neurotoxicity are also observed.

[0012] For oral administration, tacrolimus is currently formulated and marketed as soft gelatine capsules comprising the equivalent of 0.5, 1 or 5 mg anhydrous tacrolimus and marketed under the trade name Prograf® and Protropic®. The recommended initial oral dose is from about 0.1 to 0.2 mg/kg/day in patients. The dose aims at a certain trough plasma level from about 5 to about 20 ng/ml. Prograf® is indicated for the prophylaxis of organ rejection in patients receiving allogeneic liver or kidney transplants.

[0013] D1 discloses a formulation obtainable by spraying a solution of tacrolimus, PEG-24 cholesterol ether, monoglycerides and deoxycholic acid in organic solvent on non-pareil seeds and further relates to enhancement of oral bioavailability.

[0014] D2 discloses sustained release formulations obtainable by dissolving tacrolimus in molten glycerol monostearate or tetracyclering trifatty acid ester and mixing with HPM or lactose.

[0015] D3 discloses capsules comprising a solid dispersion of 20% tacrolimus in HPMC prepared by a solvent method.

[0016] D4 discloses a controlled agglomeration method for improving the bioavailability of poorly water soluble compounds in solid solutions or dispersions.

[0017] There remains a need for novel pharmaceutical compositions and/or dosage forms comprising tacrolimus exhibiting enhanced bioavailability. An increased bioavailability may allow a reduction in the dosage units taken by a patient, e.g. down to a single dose daily, and may also reduce or negate the need for food to be taken simultaneously with the dosage form thereby allowing patients more freedom on when the drug is taken. Furthermore, it is contemplated that fluctuations in the plasma concentration versus time profile may be significantly reduced. Further, enhanced bioavailability may also result in a more reproducible (i.e. less variable compared to that of Prograf®) release profile.

BRIEF SUMMARY OF THE INVENTION

[0018] The inventors have now found that the bioavailability of tacrolimus can be significantly enhanced by dissolving tacrolimus in a hydrophilic or water-miscible vehicle in an amount which is efficient for use in the preparation of a useful drug dosage form. Tacrolimus is known to have a very low solubility in water, but this invention provides pharmaceutical compositions and formulations exhibiting very fast in vitro release profiles, i.e. immediate release compositions which are contemplated having significantly increased in vivo bioavailability in patients in need thereof.

[0019] Accordingly, in a first aspect the present invention relates to a solid solution comprising tacrolimus dissolved in a mixture of polyethylene glycol and poloxamer and tacrolimus is present therein in a concentration of between about 0.01 w/w% and as much as up to about 15 w/w% to form a solid solution at ambient temperature. It is believed, that this solution is capable of releasing at least 50 w/w% of the amount of tacrolimus within about 30 minutes, when tested in any dissolution test according to USP using an aqueous dissolution medium.

[0020] In a further aspect, the invention relates to a pharmaceutical composition comprising the solid solution of tacrolimus and one or more pharmaceutically acceptable excipients, which may be fillers, disintegrants, binders or lubricants. In yet another aspect, the invention relates to dosage forms such as solid oral unit dosage forms comprising the solid solution of tacrolimus, pharmaceutically acceptable excipients and optionally pharmaceutically acceptable additive such as flavoring agents, coloring agents, taste-masking agents, pH-adjusting agents, buffering agents, preservatives, stabilizing agents, anti-oxidants, wetting agents, humidity-adjusting agents, surface-active agents, suspending agents, absorption enhancing agents and release modifying agents. Especially, the present invention relates to a dosage form comprising tacrolimus and release-modifying agents, especially dosage forms having delayed release such as solid oral unit dosage forms including enteric coating. Delaying the release of tacrolimus to the distal part of duodenum may reduce the drug related gastro-intestinal related side effects and the relatively high degree of metabolism in the

proximal part of the gastrointestinal tract (CYP3A4 mediated metabolism). Owing to the novel solid solution according to this invention, this is done without losing systemic bioavailability.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0021] As used herein, the term "active ingredient" or "active pharmaceutical ingredient" means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and are present in the drug product in a modified form intended to furnish the specified activity or effect.

[0022] In the present context, the term "hydrophilic" describes that something 'likes water', i.e. a hydrophilic molecule or portion of a molecule is one that typically is electrically polarized and capable of forming hydrogen bonds with water molecules, enabling it dissolve more readily in water than in oil or other "non-polar" solvents.

[0023] In the present context, the term "amphiphilic" describes a molecule (as a surfactant) having a polar water-soluble group attached to a water-insoluble hydrocarbon chain. Thus, one end of the molecule is hydrophilic (polar) and the other is hydrophobic (non-polar).

[0024] As used herein, the term "vehicle" means any solvent or carrier fluid in a pharmaceutical product that has no pharmacological role. For example, water is the vehicle for xilocaine and propylene glycol is the vehicle for many antibiotics.

[0025] In the present context, the term "solid dispersion" denotes a drug or active ingredient or substance dispersed on a particulate level in an inert vehicle, carrier, diluent or matrix in the solid state, i.e. usually a fine particulate dispersion.

[0026] In the present context, the term "solid solution" denotes a drug or active ingredient or substance dissolved on a molecular level in an inert vehicle, carrier, diluent or matrix in the solid state.

[0027] As used herein, the term "analogue" means a chemical compound that is structurally similar to another.

[0028] The term "drug" means a compound intended for use in diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals.

[0029] In this context, the term "dosage form" means the form in which the drug is delivered to the patient. This could be parenteral, topical, tablet, oral (liquid or dissolved powder), suppository, inhalation, transdermal, etc.

[0030] As used herein, the term "bioavailability" denotes the degree means to which a drug or other substance becomes available to the target tissue after administration.

[0031] As used herein, the term "bioequivalency" denotes a scientific basis on which generic and brand name drugs are compared with one another. For example, drugs are bioequivalent if they enter circulation at the same rate when given in similar doses under similar conditions. Parameters often used in bioequivalence studies are t_{max} , C_{max} , $AUC_{0-\infty}$, AUC_{0-t} . Other relevant parameters may be W_{50} , W_{75} and/or MRT. Accordingly, at least one of these parameters may be applied when determining whether bioequivalence is present. Furthermore, in the present context, two compositions are regarded as bioequivalent if the value of the parameter used is within 80-125% of that of Prograf® or a similar commercially available tacrolimus-containing product used in the test.

[0032] In the present context " t_{max} " denotes the time to reach the maximal plasma concentration (C_{max}) after administration; $AUC_{0-\infty}$ denotes the area under the plasma concentration versus time curve from time 0 to infinity; AUC_{0-t} denotes the area under the plasma concentration versus time curve from time 0 to time t; W_{50} denotes the time where the plasma concentration is 50% or more of C_{max} ; W_{75} denotes the time where the plasma concentration is 75% or more of C_{max} ; and MRT denotes mean residence time for tacrolimus (and/or an analogue thereof).

[0033] In this context, the term "medicine" means a compound used to treat disease, injury or pain. Medicine is justly distributed into "prophylactic," i.e. the art of preserving health, and "therapeutic", i.e. the art of restoring health.

[0034] As used herein, the term "delayed release" means a release profile of a drug from a pharmaceutical composition or formulation which, in relation to the immediate release profile, has an unchanged C_{max} , but simply a lag time from the time of administration until drug release. Accordingly, t_{max} is delayed, and $t_{1/2}$ is usually unchanged.

[0035] In this context, the term "erosion" or "eroding" means a gradual breakdown of the surface of a material or structure, for example of a tablet or the coating of a tablet.

Solid dispersion and/or Solid solution of tacrolimus

[0036] The solid solution of the invention comprises tacrolimus dissolved in a mixture of polyethylene glycol and poloxamer in a concentration of between about 0.01 w/w% and about 15 w/w%, and which solution is forming a solid solution at ambient temperature (room temperature).

[0037] The active ingredient is tacrolimus (FK-506 or FR-900506). However, within the scope of the present invention

is tacrolimus in any physical form (crystals, amorphous powder, any possible polymorphs, any possible solvates including the hydrate, anhydrate, complexes thereof etc.). Included is also any derivative or active metabolite of tacrolimus, pharmaceutically acceptable salts, solvates, complexes and prodrugs thereof.

[0038] The concentration of the active ingredient in the vehicle is at the most 15w/w%, preferably at the most 10w/w%, preferably at the most 8w/w%, more preferably at the most 6w/w%, even more preferably at the most 5w/w%, at the most 4w/w%, especially at the most 3w/w%, in particular at the most 2% w/w; and/or is at least about 0.05w/w%, preferably at least about 0.1w/w%, more preferably at least about 0.5w/w%, especially at least about 0.7w/w%, in particular at least about 1w/w%.

[0039] Physically, the combination of active ingredient and vehicle forms a solid solution, i.e. the active ingredient is dissolved in the vehicle at a molecular level. The active ingredient and the vehicle may also form a solid dispersion having therein a part of the active ingredient dissolved at a molecular level. The physical state of the dispersion and/or solution may be determined by using various techniques such as Hot Stage Microscopy (HSM), Differential Scanning Calorimetry (DSC), Scanning Electron Microscopy (SEM) optionally in combination with Energy Dispersive X-ray (EDX), and X-ray powder diffraction. In a preferred embodiment, the active ingredient is fully dissolved in the vehicle to form a solid solution at ambient temperature.

[0040] Increasing the bioavailability, the Area Under the Curve (AUC), will normally reduce the intra- and inter-variability related to absorption of a drug substance. This is particularly true; whenever the low and impaired bioavailability is a consequence of poor water solubility. It is contemplated that compositions according to the invention will provide a CV (Coefficient of Variation) on AUC data having a significantly lesser value than that of Prograf® and like products.

[0041] As mentioned hereinbefore, one of the basic features of the present invention is that it is possible to obtain an improvement in the bioavailability by oral administration of a composition of the present invention. Normally, a low bioavailability of a drug substance after oral administration is a barrier for design of a controlled or modified release composition of the drug substance due to the fact that it is almost impossible to obtain effective drug levels over a prolonged period of time. However, with the present technology it is possible to obtain a significantly improved bioavailability and thereby possible to design for example delayed release compositions.

[0042] The solid solution of the invention exhibits a very fast immediate release of tacrolimus, when a composition comprising the solution is tested in a dissolution test according to USP using an aqueous dissolution medium, and at least 50 w/w% of the active pharmaceutical ingredient is released within about 30 minutes, preferably within 20 minutes, more preferably within 15 minutes; such as at least 75 w/w% of the active pharmaceutical ingredient is released within about 40 minutes, or even better at least 90 w/w% of the active pharmaceutical ingredient is released within about 60 minutes, preferably within 45 minutes. For example, the test may be carried out according to the any method and any specifications cited in USP. Thus, the dissolution test may be carried out in an aqueous dissolution medium at a neutral or near-neutral pH, for example at pH 6.8, or at any acidic pH simulating the pH conditions in the gastrointestinal tract. However, variations with respect to the specific method employed and the ingredients contained in the dissolution medium etc. are within the scope of the present invention. A person skilled in the art will know how to carry out a suitable dissolution test e.g. with guidance from USP, Ph.Eur. and the like. Suitable conditions for the *in vitro* dissolution test are employing USP dissolution test (paddle method) and a buffer pH 7.5 containing 2.5% SDS and 1g/mL of pancreatin as dissolution medium.

[0043] In other embodiments, the following conditions are fulfilled with respect to *in vitro* dissolution tests:

i) at least about 50% w/w of the total amount of tacrolimus is released within about 10 hours such as, e.g., within about 8 hours, within about 6 hours, within about 4 hours, within about 3 hours, within about 2 hours, within about 1 hour, within about 45 min, within about 30 min or within about 15 min, when tested in an *in vitro* dissolution test and employing a dissolution medium comprising a buffer having pH 7.5

ii) at least about 50% w/w of the total amount of tacrolimus is released within about 1.5 hours such as, e.g., within about 1 hour, within about 0.75 hours, within about 0.5 hours or within about 20 minutes, when tested in an *in vitro* dissolution test and employing a dissolution medium comprising a buffer having pH 7.5.

iii) at least about 55% w/w such as, e.g., about 60% w/w or more, about 65% w/w or more, about 70% w/w or more, about 75% w/w or more or about 80% w/w or more of the total amount of tacrolimus is released within about 15 hours such as, e.g., within about 12 hours, within about 10 hours, within 8 hours or within about 6 hours, when tested in an *in vitro* dissolution test and employing a dissolution medium comprising a buffer having pH 7.5

iv) at least about 55% w/w such as, e.g., about 60% w/w or more, about 65% w/w or more, about 70% w/w or more, about 75% w/w or more or about 80% w/w or more of the total amount of tacrolimus is released within about 5 hours such as, e.g., within about 4 hours, within about 3 hours, within about 2 hours, within about 1 hours or within about 30 minutes, when tested in an *in vitro* dissolution test and employing a dissolution medium comprising a buffer having pH 7.5, and/or

v) at least about 20% w/w such as, e.g., at least about 25% w/w, at least about 30% w/w, at least about 35% w/w or at least about 40% w/w of the total amount of tacrolimus is released within the first 3 hours such as, e.g., within

the first 2 hours or within the first hour when tested in an in vitro dissolution test and employing a dissolution medium comprising a buffer having pH 7.5.

[0044] In other embodiments of the invention, the following conditions are fulfilled with respect to *in vitro* dissolution tests performed under acidic conditions:

i) at the most about 30% w/w such as, e.g., at the most about 25% w/w, at the most about 20% w/w, at the most about 15% w/w or at the most about 14% w/w of tacrolimus is released within 2 hours in an in vitro dissolution test employing a dissolution medium having a pH of at the most about 5 such as, e.g. at the most about 4.5, at the most about 4, at the most about 3.5, at the most about 3, at the most about 2 or at the most about 1.5;

ii) at the most about 10% w/w such as, e.g., at the most about 7.5% w/w, at the most about 5% w/w or at the most about 2.5% w/w of tacrolimus is released within 2 hours in an in vitro dissolution test employing a dissolution medium having a pH of at the most about 5 such as, e.g. at the most about 4.5, at the most about 4, at the most about 3.5, at the most about 3, at the most about 2 or at the most about 1.5;

iii) at the most about 60% w/w such as, e.g., at the most about 50% w/w, at the most about 40% w/w or at the most about 30% w/w of tacrolimus is released within 15 hours such as, e.g., within about 12 hours, when tested in an in vitro dissolution test employing a dissolution medium having a pH of at the most about 4.5 such as, e.g. at the most about 4.0, at the most about 3.5, at the most about 3, at the most about 2 or at the most about 1.5;

iv) at the most about 40% w/w such as, e.g., at the most about 30% w/w, at the most about 25% w/w or at the most about 20% w/w of tacrolimus is released within 6 hours when tested in an in vitro dissolution test employing a dissolution medium having a pH of at the most about 4.5 such as, e.g. at the most about 4.0, at the most about 3.5, at the most about 3, at the most about 2 or at the most about 1.5, and/or v) at the most about 30% w/w such as, e.g., at the most about 25% w/w, at the most about 20% w/w or at the most about 15% w/w of tacrolimus is released within 4 hours when tested in an in vitro dissolution test employing a dissolution medium having a pH of at the most about 4.5 such as, e.g. at the most about 4.0, at the most about 3.5, at the most about 3, at the most about 2 or at the most about 1.5.

[0045] Vehicles to be used according to this invention are selected from mixtures of polyethylene glycol and poloxamer.

[0046] The vehicle is a polyethylene glycol (PEG), in particular a PEG having an average molecular weight of at least 1500, preferably at least 3000, more preferably at least 4000, especially at least 6000, mixed with a poloxamer, in a proportion (on a weight/weight basis) of between 1:3 and 10:1, preferably between 1:1 and 5:1, more preferably between 3:2 and 4:1, especially between 2:1 and 3:1, in particular about 7:3. A specific example of a useful mixture is a mixture of PEG6000 and poloxamer 188 in the ratio 7:3.

[0047] For polyethylene glycols (PEG), the melting point (freezing point or pour point) increases as the average molecular weight increases. For example, PEG 400 is in the range of 4-8°C, PEG 600 is in the range of 20-25°C, PEG1500 is in the range of 44-48°C, PEG2000 is about 52°C, PEG 4000 is about 59°C, PEG 6000 is about 65°C and PEG 8000 is about 61°C.

[0048] Useful poloxamers (also denoted polyoxypropylene-polyoxyethylene block copolymers) are for example poloxamer 188, poloxamer 237, poloxamer 338 or poloxamer 407 or other block copolymers of ethylene oxide and propylene oxide such as the Pluronic® and/or Tetronic® series. Suitable block copolymers of the Pluronic® series include polymers having a molecular weight of about 3,000 or more such as, e.g. from about 4,000 to about 20,000 and/or a viscosity (Brookfield) from about 200 to about 4,000 cps such as, e.g., from about 250 to about 3,000 cps. Suitable examples include Pluronic® F38, P65, P68LF, P75, F77, P84, P85, F87, F88, F98, P103, P104, P105, F108, P123, F123, F127, 10R8, 17R8, 25R5, 25R8 etc. Suitable block copolymers of the Tetronic® series include polymers having a molecular weight of about 8,000 or more such as, e.g., from about 9,000 to about 35,000 and/or a viscosity (Brookfield) of from about 500 to about 45,000 cps such as, e.g., from about 600 to about 40,000. The viscosities given above are determined at 60°C for substances that are pastes at room temperature and at 77 °C for substances that are solids at room temperature.

[0049] In a preferred embodiment of the present invention, the poloxamer is poloxamer 188, which has an average molecular weight of about 8400 and a melting point of about 50-54°C.

Pharmaceutical compositions

[0050] The pharmaceutical composition of the invention comprises the solid solution of the invention and one or more pharmaceutically acceptable excipients, for example one or more excipients useful as fillers, disintegrants, binders and/or lubricants.

[0051] Preferably, the pharmaceutical composition of the invention is in particulate form, for example in powder form. Preferably, the particulate material obtained is a free-flowing powder and therefore readily processable into e.g. solid

dosage forms such as tablets, capsules or sachets. Normally, the particulate material has properties that are suitable in order to manufacture tablets by direct compression without addition of large amounts of further additives. A suitable test for testing the flowability of the particulate material is the method described in Ph.Eur. and measuring the flow rate of the material out of a funnel with a nozzle (orifice) diameter of 10.0 mm.

[0052] The particles may have a geometric weight mean diameter d_{gw} from about 10 μm to about 2000 μm , preferably from about 20 μm to about 2000 μm , more preferably from about 30 μm to about 2000 μm , more preferably from about 50 μm to about 2000 μm , more preferably from about 60 μm to about 2000 μm , more preferably from about 75 μm to about 2000 μm , more preferably from about 100 μm to about 1500 μm , more preferably from about 100 μm to about 1000 μm , more preferably from about 100 μm to about 700 μm , more preferably from about 50 μm to about 400 μm , more preferably from about 50 μm to about 350 μm , even more preferably from about 50 μm to about 300 μm , especially from about 50 μm to about 250 μm or, in particular, from about 100 μm to about 300 μm . In a preferred embodiment of the invention, the particles have a geometric weight mean diameter d_{gw} from about 50 μm to about 300 μm .

[0053] Examples on suitable excipients for use in a composition or solid dosage form according to the invention include fillers, diluents, disintegrants, binders, lubricants etc. or mixture thereof. As the composition or solid dosage form according to the invention may be used for different purposes, the choice of excipients is normally made taken such different uses into considerations. Other pharmaceutically acceptable excipients for suitable use are e.g. acidifying agents, alkalizing agents, preservatives, antioxidants, buffering agents, chelating agents, coloring agents, complexing agents, emulsifying agents and/or solubilizing agents, flavors and perfumes, humectants, sweetening agents, wetting agents etc.

[0054] Examples on suitable fillers, diluents and/or binders include lactose (e.g. spray-dried lactose, α -lactose, β -lactose, Tabletose®, various grades of Pharmatose®, Microtose® or Fast-Floc®), microcrystalline cellulose (various grades of Avicel®, Elcema®, Vivacel®, Ming Tai® or Solka-Floc®), hydroxypropylcellulose, L-hydroxypropylcellulose (low substituted), hydroxypropyl methylcellulose (HPMC) (e.g. Methocel E, F and K, Metolose SH of Shin-Etsu, Ltd, such as, e.g. the 4,000 cps grades of Methocel E and Metolose 60 SH, the 4,000 cps grades of Methocel F and Metolose 65 SH, the 4,000, 15,000 and 100,000 cps grades of Methocel K; and the 4,000, 15,000, 39,000 and 100,000 grades of Metolose 90 SH), methylcellulose polymers (such as, e.g., Methocel A, Methocel A4C, Methocel A15C, Methocel A4M), hydroxyethylcellulose, sodium carboxymethylcellulose, carboxymethylene, carboxymethylhydroxyethylcellulose and other cellulose derivatives, sucrose, agarose, sorbitol, mannitol, dextrans, maltodextrins, starches or modified starches (including potato starch, maize starch and rice starch), calcium phosphate (e.g. basic calcium phosphate, calcium hydrogen phosphate, dicalcium phosphate hydrate), calcium sulfate, calcium carbonate, sodium alginate, collagen etc.

[0055] Specific examples of diluents are e.g. calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, microcrystalline cellulose, powdered cellulose, dextrans, dextrin, dextrose, fructose, kaolin, lactose, mannitol, sorbitol, starch, pregelatinized starch, sucrose, sugar etc.

[0056] Specific examples of disintegrants are e.g. alginic acid or alginates, microcrystalline cellulose, hydroxypropyl cellulose and other cellulose derivatives, croscarmellose sodium, crospovidone, polacrillin potassium, sodium starch glycolate, starch, pregelatinized starch, carboxymethyl starch (e.g. Primogel® and Explotab®) etc.

[0057] Specific examples of binders are e.g. acacia, alginic acid, agar, calcium carrageenan, sodium carboxymethylcellulose, microcrystalline cellulose, dextrin, ethylcellulose, gelatin, liquid glucose, guar gum, hydroxypropyl methylcellulose, methylcellulose, pectin, PEG, povidone, pregelatinized starch etc.

[0058] Glidants and lubricants may also be included in the composition. Examples include stearic acid, magnesium stearate, calcium stearate or other metallic stearate, talc, waxes and glycerides, light mineral oil, PEG, glyceryl behenate, colloidal silica, hydrogenated vegetable oils, corn starch, sodium stearyl fumarate, polyethylene glycols, alkyl sulfates, sodium benzoate, sodium acetate etc.

[0059] Other excipients which may be included in a composition or solid dosage form of the invention are e.g. flavoring agents, coloring agents, taste-masking agents, pH-adjusting agents, buffering agents, preservatives, stabilizing agents, anti-oxidants, wetting agents, humidity-adjusting agents, surface-active agents, suspending agents, absorption enhancing agents, agents for modified release etc.

[0060] Other additives in a composition or a solid dosage form according to the invention may be antioxidants like e.g. ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorous acid, monothioglycerol, potassium metabisulfite, propyl gallate, sodium formaldehyde sulfoxylate, sodium metabisulfite, sodium thiosulfate, sulfur dioxide, tocopherol, tocopherol acetate, tocopherol hemisuccinate, TPGS or other tocopherol derivatives, etc. The carrier composition may also contain e.g. stabilising agents. The concentration of an antioxidant and/or a stabilizing agent in the carrier composition is normally from about 0.9 % w/w to about 5% w/w.

[0061] The pharmaceutical composition or solid dosage form according to the invention may also include one or more surfactants or substances having surface-active properties. It is contemplated that such substances are involved in the wetting of the slightly soluble active substance and thus, contributes to improved solubility characteristics of the active substance. Suitable excipients for use in a composition or a solid dosage form according to the invention are surfactants such as, e.g., amphiphilic surfactants as those disclosed in WO 00/50007 in the name of Lipocine, Inc.

[0062] Examples of suitable substances useful as surfactants are

- i) polyethoxylated fatty acids such as, e.g. fatty acid mono- or diesters of polyethylene glycol or mixtures thereof such as, e.g. mono - or diesters of polyethylene glycol with lauric acid, oleic acid, stearic acid, myristic acid, ricinoleic acid, and the polyethylene glycol may be selected from PEG 4, PEG 5, PEG 6, PEG 7, PEG 8, PEG 9, PEG 10, PEG 12, PEG 15, PEG 20, PEG 25, PEG 30, PEG 32, PEG 40, PEG 45, PEG 50, PEG 55, PEG 100, PEG 200, PEG 400, PEG 600, PEG 800, PEG 1000, PEG 2000, PEG 3000, PEG 4000, PEG 5000, PEG 6000, PEG 7000, PEG 8000, PEG 9000, PEG 1000, PEG 10,000, PEG 15,000, PEG 20,000, PEG 35,000,
- ii) polyethylene glycol glycerol fatty acid esters, i.e. esters like the above-mentioned but in the form of glyceryl esters of the individual fatty acids;
- iii) glycerol, propylene glycol, ethylene glycol, PEG or sorbitol esters with e.g. vegetable oils like e.g. hydrogenated castor oil, almond oil, palm kernel oil, castor oil, apricot kernel oil, olive oil, peanut oil, hydrogenated palm kernel oil and the like,
- iv) polyglycerized fatty acids like e.g. polyglycerol stearate, polyglycerol oleate, polyglycerol ricinoleate, polyglycerol linoleate,
- v) propylene glycol fatty acid esters such as, e.g. propylene glycol monolaurate, propylene glycol ricinoleate and the like,
- vi) mono- and diglycerides like e.g. glyceryl monooleate, glyceryl dioleae, glyceryl mono- and/or dioleate, glyceryl caprylate, glyceryl caprate etc.;
- vii) sterol and sterol derivatives;
- viii) polyethylene glycol sorbitan fatty acid esters (PEG-sorbitan fatty acid esters) such as esters of PEG with the various molecular weights indicated above, and the various Tween ® series;
- ix) polyethylene glycol alkyl ethers such as, e.g. PEG oleyl ether and PEG lauryl ether;
- x) sugar esters like e.g. sucrose monopalmitate and sucrose monolaurate;
- xi) polyethylene glycol alkyl phenols like e.g. the Triton® X or N series;
- xii) polyoxyethylene-polyoxypropylene block copolymers such as, e.g., the Pluronic® series, the Synperonic® series, Emkalyx®, Lutrol®, Supronic® etc. The generic term for these polymers is "poloxamers" and relevant examples in the present context are Poloxamer 105, 108, 122, 123, 124, 181, 182, 183, 184, 185, 188, 212, 215, 217, 231, 234, 235, 237, 238, 282, 284, 288, 331, 333, 334, 335, 338, 401, 402, 403 and 407;
- xiii) sorbitan fatty acid esters like the Span® series or Ariacel® series such as, e.g. sorbinan monolaurate, sorbitan monopalmitate, sorbitan monooleate, sorbitan monostearate etc.;
- xiv) lower alcohol fatty acid esters like e.g. oleate, isopropyl myristate, isopropyl palmitate etc.;
- xv) ionic surfactants including cationic, anionic and zwitterionic surfactants such as, e.g. fatty acid salts, bile salts, phospholipids, phosphoric acid esters, carboxylates, sulfates and sulfonates etc.

[0063] When a surfactant or a mixture of surfactants is present in a composition or a solid dosage form of the invention, the concentration of the surfactant(s) is normally in a range of from about 0.1 - 80% w/w such as, e.g., from about 0.1 to about 20% w/w, from about 0.1 to about 15% w/w, from about 0.5 to about 10% w/w, or alternatively, from about 0.10 to about 80% w/w such as, e.g. from about 10 to about 70% w/w, from about 20 to about 60% w/w or from about 30 to about 50% w/w.

[0064] In a specific aspect of the invention, the at least one of the one or more pharmaceutically acceptable excipient is selected from the group consisting of silica acid or a derivative or salt thereof including silicates, silicon dioxide and polymers thereof; magnesium aluminosilicate and/or magnesium aluminometasilicate, bentonite, kaolin, magnesium trisilicate, montmorillonite and/or saponite.

[0065] Such materials are especially useful as a sorption material for oils or oily materials in pharmaceuticals, cosmetics and/or foodstuff. In a specific embodiment, the material is used as a sorption material for oils or oily materials in pharmaceuticals. The material that has the ability to function as a sorption material for oils or oily materials is also denoted "oil sorption material". Furthermore, in the present context the term "sorption" is used to denote "absorption" as well as "adsorption". It should be understood that whenever one of the terms is used it is intended to cover the phenomenon absorption as well as adsorption.

[0066] Notably, the pharmaceutically acceptable excipient may comprise a silica acid or a derivative or salt thereof such as, e.g., silicon dioxide or a polymer thereof as a pharmaceutically acceptable excipient. Dependent on the quality employed a silicon dioxide may be a lubricant or it may be an oil sorption material. Qualities fulfilling the latter function seem to be most important.

[0067] In a specific embodiment, the composition or solid dosage form according to invention comprises a pharmaceutically acceptable excipient that is a silicon dioxide product that has properties corresponding to Aeroperl® 300 (available from Degussa, Frankfurt, Germany). As it appears from the examples herein, a very suitable material is Aeroperl® 300 (including materials with properties like or corresponding to those of Aeroperl® 300).

[0068] Use of an oil sorption material in compositions or dosage forms according to the invention is very advantageous for the preparation of pharmaceutical, cosmetic, nutritional and/or food compositions, wherein the composition comprises

oil or an oily material. One of the advantages is that it is possible to incorporate a relatively large amount of oil and oily material and still have a material that is solid. Thus, it is possible to prepare solid compositions with a relatively high load of oil or oily materials by use of an oil sorption material according to the invention. Within the pharmaceutical field it is an advantage to be able to incorporate a relatively large amount of an oil or an oily-like material in a solid composition especially in those situation where the active substance does not have suitable properties with respect to water solubility (e.g. poor water solubility), stability in aqueous medium (i.e. degradation occurs in aqueous medium), oral bioavailability (e.g. low bioavailability) etc., or in those situations where it is desired to modify the release of an active substance from a composition in order to obtain a controlled, delayed, sustained and/or pulsed delivery of the active substance. Thus, in a specific embodiment it is used in the preparation of pharmaceutical compositions.

[0069] The oil sorption material for use in the processing into solid compositions normally absorbs about 5% w/w or more, such as, e.g., about 10% w/w or more, about 15% w/w or more, about 20% w/w or more, about 25% w/w or more, about 30% w/w or more, about 35% w/w or more, about 40% w/w or more, about 45% w/w or more, about 50 w/w or more, about 55% w/w or more, about 60% w/w or more, about 65% w/w or more, about 70% w/w or more, about 75% w/w or more, about 80% w/w or more, about 85% w/w or more, about 90% w/w or more or about 95% w/w or more of an oil or an oily material and is still a solid material.

[0070] As it appears from the examples herein the bioavailability obtained after administration of a composition according to the invention is markedly improved. Thus, in specific embodiments, the $AUC/AUC_{Prograf^{\text{®}}}$ value is at least about 1.5 such as about 1.75 or more, about 1.8 or more, about 1.9 or more, about 2.0 or more, about 2.5 or more, about 2.75 or more, about 3.0 or more, about 3.25 or more, about 3.5 or more, about 3.75 or more, about 4.0 or more, about 4.25 or more, about 4.5 or more, about 4.75 or more or about 5.0 or more, the AUC values being determined under similar conditions.

[0071] After oral administration of a pharmaceutical composition according to the present invention it is contemplated that the plasma concentration versus time profile show an extended period of time in which the plasma concentration is maintained within the therapeutic window (i.e. the plasma concentration leads to a therapeutic effect) without leading to serious unwanted side effects. Thus, a reduction in peak concentration may be observed.

[0072] However, a reduction in peak concentration may not lead to a decrease in therapeutic effect as long as the plasma concentration of tacrolimus is maintained within the therapeutic window.

[0073] It is contemplated that the need for simultaneous food intake in order to secure a sufficient uptake of tacrolimus is significantly reduced or even completely abolished, when administering a pharmaceutical composition or dosage form of the present invention.

[0074] Thus, the pharmaceutical compositions of the invention provide significant higher bioavailability of tacrolimus, which may reduce the number of daily administered dosage units, and reduce or abolish the need for administration in connection with food intake, which provide for a higher degree of freedom for the recipient of the pharmaceutical compositions, and consequently the patients acceptance and/or compliance may be significantly improved. Furthermore, the compositions provide a significant reduction in side effects, especially side effect related to a high peak concentration (such as, e.g., nephro- and neuro-toxicity, diarrhea, constipation, abdominal pain, nausea etc) and provide for an extended release of tacrolimus leading to a better therapy.

[0075] One of the major challenges with respect to formulation of tacrolimus compositions is to avoid an adverse food effect. In general, tacrolimus is much better absorbed when it is administered orally without food. A great variation in bioavailability is therefore seen following administration with or without food. This dependency makes it difficult to give precise guidelines as to how large a dose that should be administered and, furthermore, it requires information to the patient about the dosing regime. The present invention aims at providing compositions wherein the adverse food effect is reduced. Thus, the present invention provides a composition, which does not exhibit a significant adverse food effect after administration of the composition to a mammal in need of such a treatment as evidenced by a value of $(AUC_{\text{fed}}/VAUC_{\text{fasted}})$ of at least about 0.85 with a lower 90% confidence limit of at least 0.75.

[0076] More specifically, a pharmaceutical composition according to the invention has a value of $(AUC_{\text{fed}}/AUC_{\text{fasted}})$ of about 0.9 or more such as, e.g., about 0.95 or more, about 0.97 or more or about 1 or more such as, e.g., up to about 1.1 or up to about 1.2.

[0077] Apart from tacrolimus, the composition of the invention may also comprise a further therapeutically, prophylactically and/or diagnostically active substance. Notably combinations of tacrolimus with at least one of the following active substances are of interest: Substances that are indicated for use in connection with organ transplantation such as, e.g., steroids, calcineurin inhibitors and/or anti-proliferative agents. Specific examples include prednisone, prednisolone, methylprednisone, cyclosporin, mycophenolate, azathioprine, sirolimus, everolimus, mycophenolate sodium, and FTY720 (developed by the pharmaceutical company Novartis).

Dosage forms

[0078] Useful dosage forms of the invention are solid oral dosage forms comprising the solid solution and one or more

pharmaceutically acceptable excipients, preferably unit dosage forms.

[0079] The pharmaceutical composition according to the invention is in particulate form and may be employed as such. However, in many cases it is more convenient to present the composition in the form of granules, pellets, microspheres, nanoparticles and the like or in the form of solid dosage forms including tablets, capsules and sachets and the like.

[0080] A solid dosage form according to the invention may be a single unit dosage form or it may in the form of a polydepot dosage form contain a multiplicity of individual units such as, e.g., pellets, beads and/or granules.

[0081] The dosage forms may further comprise pharmaceutically acceptable additives such as flavoring agents, coloring agents, taste-masking agents, pH-adjusting agents, buffering agents, preservatives, stabilizing agents, anti-oxidants, wetting agents, humidity-adjusting agents, surface-active agents, suspending agents, absorption enhancing agents and release modifying agents.

[0082] In a preferred embodiment, the dosage form comprises silica acid or a derivative or salt thereof including silicates, silicon dioxide and polymers thereof; and/or magnesium aluminosilicate and/or magnesium aluminometasilicate, bentonite, kaolin, magnesium trisilicate, montmorillonite and/or saponite. A particularly useful excipient to be included in the dosage forms is any silicon dioxide product having properties corresponding to Aeroperi® 300 (available from Degussa, Frankfurt, Germany).

[0083] A solid dosage form according to the present invention comprises a pharmaceutical composition in particulate form as described above. The details and particulars disclosed under this main aspect of the invention apply *mutatis mutandis* to the other aspects of the invention. Accordingly, the properties with respect to increase in bioavailability, changes in bioavailability parameters, reduction in adverse food effect as well as release of tacrolimus and/or an analogue thereof etc. described and/or claimed herein for pharmaceutical compositions in particulate form are analogues for a solid dosage form according to the present invention.

[0084] Normally, the concentration of the pharmaceutical composition in particulate form is in a range of from about 5 to 100% w/w such as, e.g., from about 10% to about 90% w/w, from about 15% to about 85% w/w, from about 20% to about 80% w/w, from about 25% to about 80% w/w, from about 30% to about 80% w/w, from about 35% to about 80% w/w, from about 40% to about 75% w/w, from about 45% to about 75% w/w or from about 50% to about 70% w/w of the dosage form. In an embodiment of the invention, the concentration of the pharmaceutical composition in particulate form is 50% w/w or more of the dosage form.

[0085] A solid dosage form according to the invention is obtained by processing the particulate material according to the invention by means of techniques well-known to a person skilled in the art. Normally, it involves further addition of one or more of the pharmaceutically acceptable excipients mentioned herein.

[0086] The composition or solid dosage form according to the invention may be designed to release tacrolimus in any suitable manner provided that the increase in bioavailability is present. Thus, the active substance may be released relatively fast in order to obtain an enhanced on-set of action, it may be released so as to follow zero or first order kinetics or it may be released in a modified manner in order to obtain a predetermined pattern of release. All of these ways are considered controlled manners. Plain formulations are also within the scope of the present invention.

[0087] The recommended dosage range for Prograf® is 0.1 to 0.2 mg/kg/day given every 12 hours in two divided doses. More importantly the blood levels has to be monitored. The typical level for 1 - 3 months is 7 -20 ng/mL and 4 - 12 months the levels should be 5 - 15 ng/mL. This is only guiding values and may vary from types of transplant and ethnicity.

[0088] The following data have been found for kidney transplant patients:

Time After Transplant	Dose (mg/kg)	Caucasian n=114 Trough Concentrations (ng/mL)	Dose (mg/kg)	Black n=56 Trough Concentrations (ng/mL)
Day 7	0.18	12.0	0.23	10.9
Month 1	0.17	12.8	0.26	12.9
Month 6	0.14	11.8	0.24	11.5
Month 12	0.13	10.1	0.19	11.0

[0089] The contemplated dosage recommendation for products of the present invention will be from 0.02 mg/kg/day to 0.15 mg/kg/day, dosed once a day.

Enteric coatings - delayed release

[0090] It has been found that the efficacy of oral tacrolimus treatment can be greatly improved through proper design of the tacrolimus release profile. On the one hand relatively high doses of tacrolimus are required to avoid transplant rejection and on the other hand side effects often get too pronounced even at therapeutically relevant levels. Thus, the

side effects such as acute nausea, vomiting, nephrotoxicity and neurotoxicity are directly linked to high peak plasma concentrations. This link has been demonstrated in dogs. In those cases where a lower dose has been used in order to avoid a high peak level, the dose-dependent side effects almost cease to occur at a certain threshold level and, if they occurred, they were much less pronounced. However, due to the decrease in dose (without increasing the bioavailability) the therapeutically effective level is only maintained for a short duration of time. The present invention addresses this problem by providing a pharmaceutical composition or dosage form containing tacrolimus, wherein the release of tacrolimus is designed to avoid high peak concentrations and at the same time, the composition is designed so that the overall bioavailability is maintained or increased as compared to commercially available tacrolimus-containing dosage forms. Moreover, by delaying the release of tacrolimus and at the same time provide a composition wherein tacrolimus is at least partly in dissolved form, it is possible to obtain a significant absorption in the distal part of the gastrointestinal tract.

[0091] Thus, the dosage form of the invention may further comprise one or more release modifying agents selected from the group consisting of water-miscible polymers, water-insoluble polymers, oils and oily materials.

[0092] The water-insoluble polymer may be ethyl cellulose, cellulose acetate, cellulose nitrate, and mixtures thereof. The water-miscible polymer may also be a cellulose derivative selected from the group consisting of hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), methylcellulose, sodium carboxymethylcellulose, hydroxyethyl cellulose, poloxamers, polyoxyethylene stearates, poly- ϵ -caprolactone, polyvinylpyrrolidone (PVP), polyvinylpyrrolidone-polyvinylacetate copolymer PVP-PVA, polymethacrylic polymers and polyvinyl alcohol (PVA), poly(ethylene oxide) (PEO) and mixtures thereof. Examples of especially useful polymethacrylic polymers are Eudragit® RS, Eudragit® RL, Eudragit® NE and Eudragit® E.

[0093] The oil or oily material may be hydrophilic and hydrophobic oils or oily materials.

[0094] Hydrophilic oil or oily material may be polyether glycols such as polypropylene glycols; polyoxyethylenes; polyoxypropylenes; poloxamers; polyglycolized glycerides such as Gelucire®, for example Gelucire® 50/13, Gelucire® 44/14, Gelucire® 50/10, Gelucire® 62/05 and mixtures thereof.

[0095] Hydrophobic oil or oily material may have a melting point of at least about 20°C. Useful examples are straight chain saturated hydrocarbons, sorbitan esters, paraffins; fats and oils such as cacao butter, beef tallow, lard, polyether glycol esters; higher fatty acid such as stearic acid, myristic acid, palmitic acid, higher alcohols such as cetanol, stearyl alcohol, low melting point waxes such as glyceryl monostearate, glyceryl monooleate, hydrogenated tallow, myristyl alcohol, stearyl alcohol, substituted and/or unsubstituted monoglycerides, substituted and/or unsubstituted diglycerides, substituted and/or unsubstituted triglycerides, yellow beeswax, white beeswax, carnauba wax, castor wax, japan wax, acetylate monoglycerides; NVP polymers, PVP polymers, acrylic polymers, and mixtures thereof.

[0096] The oil or oily-like material may also be a sorbitan ester such as, e.g., sorbitan di-isostearate, sorbitan dioleate, sorbitan monolaurate, sorbitan monoisostearate, sorbitan monooleate, sorbitan monopalmitate, sorbitan monostearate, sorbitan sesqui-isostearate, sorbitan sesquioleate, sorbitan sesquisteate, sorbitan tri-isostearate, sorbitan trioleate, sorbitan tristearate or mixtures thereof.

[0097] The oil or oily-like material may of course comprise a mixture of different oils or oily-like materials such as, e.g., a mixture of hydrophilic and/or hydrophobic materials.

[0098] Other suitable oils or oily-like materials may be solvents or semi-solid excipients like, e.g. propylene glycol, polyglycolised glycerides including Gelucire 44/14, complex fatty materials of plant origin including theobroma oil, carnauba wax, vegetable oils like e.g. almond oil, coconut oil, corn oil, cottonseed oil, sesame oil, soya oil, olive oil, castor oil, palm kernels oil, peanut oil, rape oil, grape seed oil etc., hydrogenated vegetable oils such as, e.g. hydrogenated peanut oil, hydrogenated palm kernels oil, hydrogenated cottonseed oil, hydrogenated soya oil, hydrogenated castor oil, hydrogenated coconut oil; natural fatty materials of animal origin including beeswax, lanolin, fatty alcohols including cetyl, stearyl, lauric, myristic, palmitic, stearic fatty alcohols; esters including glycerol stearate, glycol stearate, ethyl oleate, isopropyl myristate; liquid interesterified semi-synthetic glycerides including Miglycol 810/812; amide or fatty acid alcolamides including stearamide ethanol, diethanolamide of fatty coconut acids, acetic acid esters of mono and diglycerides, citric acid esters of mono and di-glycerides, lactic acid esters of mono and diglycerides, mono and diglycerides, poly-glycerol esters of fatty acids, poly-glycerol poly-ricinoleate, propylene glycol esters of fatty acids, sorbitan monostearates, sorbitan tristearates, sodium stearyl lactylates, calcium stearyl lactylates, diacetyl tartaric acid esters of mono and di-glycerides etc.

[0099] A delayed release of active ingredient is desired in order to increase the bioavailability of active ingredient by delivering the ingredient in the gastrointestinal tract, i.e. the release predominantly takes place after passage of the stomach. For example, the dosage form of the present invention may be designed in order to release, after oral administration to a mammal in need thereof, at the most about 10 w/w%, preferably at the most about 7.5 w/w%, more preferably at the most about 5 w/w%, especially at the most about 2 w/w% of the total amount of active ingredient within the first 3 hours, preferably within 2 hours, more preferably within 1 hours, in particular within about 30 minutes after administration.

[0100] Further, the solid dosage form of the invention may, upon oral administration to a mammal in need thereof, release at least about 50 w/w% of the active ingredient within 24 hours, preferably within about 20 hours, more preferably within about 18 hours, especially within about 15 hours, in particular within about 12 hours.

[0101] Delayed release is mainly brought about by some kind of enteric coating. Whereas semipermeable coating will show some kind of delayed release, it may not precisely enough "delay" release. Additionally it requires a certain amount of time to release the content. The coating sought for this invention, is a pH dependant coating. This type of coating is very resistant to release of drug until a certain pH is reached. Within a small increment in the pH value, i.e.

within an increase in pH of about 0.2 to 0.4, the film alters properties and becomes permeable.

[0102] Accordingly, the solid dosage forms of the invention may exhibit a delayed release of active ingredient by means of an enteric coating using a water-miscible polymer having a pH-dependant solubility in water. Examples of pH-sensitive polymers, which are relatively insoluble and impermeable at the pH of the stomach, but which are more soluble and permeable at the pH of the small intestine and colon include, but are not limited to, polyacrylamides; phthalate derivatives such as acid phthalates of carbohydrates including amylose acetate phthalate, cellulose acetate phthalate, cellulose acetate terephthalate, cellulose acetate isophthalate, other cellulose ester phthalates, cellulose ether phthalates, hydroxypropyl cellulose phthalate, hydroxypropylcellulose acetate phthalate, hydroxypropyl ethylcellulose phthalate, hydroxypropyl methylcellulose phthalate (HMPCP), methylcellulose phthalate, methyl cellulose acetate phthalate, polyvinyl acetate phthalate, polyvinyl acetate hydrogen phthalate, sodium cellulose acetate phthalate, starch acid phthalate; phthalates of other compounds including polyvinyl acetate phthalate (PVAP); other cellulose derivatives including hydroxypropyl methylcellulose acetate succinate (HPMCAS), carboxymethylcellulose, cellulose acetate trimellitate; alginates; carbomers; polyacrylic acid derivatives such as acrylic acid and acrylic ester copolymers, polymethacrylic acid and esters thereof, poly acrylic methacrylic acid copolymers, methacrylic acid copolymers (for example Eudragit® L and Eudragit® S); styrene-maleic acid dibutyl phthalate copolymer, styrene-maleic acid polyvinylacetate phthalate copolymer, styrene and maleic acid copolymers; shellac, starch glycolate; polacrylin; vinyl acetate and crotonic acid copolymers and mixtures thereof. pH-sensitive polymers of specific interest include shellac; phthalate derivatives, particularly cellulose acetate phthalate, polyvinylacetate phthalate, and hydroxypropylmethylcellulose phthalate; polyacrylic acid derivatives, particularly polymethyl methacrylate blended with acrylic acid and acrylic ester copolymers; and vinyl acetate and crotonic acid copolymers.

[0103] A first delayed release embodiment according to the invention is a "pH-dependent coated dosage form" such as, e.g., a tablet or a capsule. In the case of a tablet it comprises a tablet core comprising tacrolimus e.g. in a solid solution/dispersion as a multiparticulate product, a controlled release matrix of e.g. HPMC, a disintegrant, a lubricant, and one or more pharmaceutical carriers, such core being coated with a material, preferably a polymer, which is substantially insoluble and impermeable at the pH of the stomach, and which is more soluble and permeable at the pH of the small intestine. Preferably, the coating polymer is substantially insoluble and impermeable at pH <5.0, and water-soluble at pH >5.0. The tablet core may be coated with an amount of polymer sufficient to assure that substantially no release of tacrolimus from the dosage form occurs until the dosage form has exited the stomach and has resided in the small intestine for about 15 minutes or greater, preferably about 30 minutes or greater, thus assuring that minimal tacrolimus is released in the duodenum. Mixtures of a pH-sensitive polymer with a water-insoluble polymer may also be employed. Tablets are coated with an amount of polymer comprising from about 10% to about 80% of the weight of the tacrolimus-containing tablet core. Preferred tablets are coated with an amount of polymer comprising about 15% to about 50% of the weight of the tacrolimus tablet core.

[0104] pH-sensitive polymers which are very insoluble and impermeable at the pH of the stomach, but which are more soluble and permeable at the pH of the small intestine and colon include polyacrylamides, phthalate derivatives such as acid phthalates of carbohydrates, amylose acetate phthalate, cellulose acetate phthalate, other cellulose ester phthalates, cellulose ether phthalates, hydroxypropylcellulose phthalate, hydroxypropylethylcellulose phthalate, hydroxypropylmethylcellulose phthalate, methylcellulose phthalate, polyvinyl acetate phthalate, polyvinyl acetate hydrogen phthalate, sodium cellulose acetate phthalate, starch acid phthalate, styrene-maleic acid dibutyl phthalate copolymer, styrene-maleic acid polyvinylacetate phthalate copolymer, styrene and maleic acid copolymers, polyacrylic acid derivatives such as acrylic acid and acrylic ester copolymers, polymethacrylic acid and esters thereof, poly acrylic methacrylic acid copolymers, shellac, and vinyl acetate and crotonic acid copolymers.

[0105] Preferred pH-sensitive polymers include shellac; phthalate derivatives, particularly cellulose acetate phthalate, polyvinylacetate phthalate, and hydroxypropylmethylcellulose phthalate; polyacrylic acid derivatives, particularly polymethyl methacrylate blended with acrylic acid and acrylic ester copolymers; and vinyl acetate and crotonic acid copolymers.

[0106] The delay time before release of tacrolimus, after the "pH-dependent coated tablet" dosage form has exited the stomach, may be controlled by choice of the relative amounts of Eudragit-L® and Eudragit-S® in the coating, and by choice of the coating thickness. Eudragit-L® films dissolve above pH 6.0, and Eudragit-S® films dissolve above 7.0, and mixtures dissolve at an intermediate pH. Since the pH of the duodenum is approximately 6.0 and the pH of the colon is approximately 7.0, coatings composed of mixtures of Eudragit-L® and Eudragit-S® provide protection of the duodenum from tacrolimus. If it is desired to delay release of tacrolimus until the tacrolimus-containing "pH-dependent coated tablet" has reached the colon, Eudragit-S® may be used as the coating material, as described by Dew et al. (Br. J. Clin. Pharmac. 14 (1982) 405-408). In order to delay the release of tacrolimus for about 15 minutes or more, preferably 30 minutes or more, after the dosage form has exited the stomach, preferred coatings comprise from about 9:1 to about 1:9 Eudragit-

L® /Eudragit-S®, more preferably from about 9:1 to about 1:4 Eudragit-L® /Eudragit-S®. The coating may comprise from about 3% to about 70% of the weight of the uncoated tablet core. Preferably, the coating comprises from about 5% to about 50% of the weight of the tablet core.

[0107] The release of the active substance from a composition having a delayed release coating could also be an enzymatic reaction, if for example Zein or mono/di-glyceride mixtures are employed as coating material.

Manufacture of the compositions and dosage forms of the invention

[0108] The present invention also provides a method for the preparation of the solid solution of the invention, the method comprising the step of dissolving tacrolimus in a polyethylene glycol and poloxamer to obtain a solid solution at ambient temperature.

[0109] The pharmaceutical compositions of the invention may be prepared by any convenient method such as, e.g. granulation, mixing, spray drying etc. An example of a useful method is the controlled agglomeration method disclosed in WO 03/004001, i.e. a method enabling a controlled growth in particle size. The method involves spraying a first composition comprising an active ingredient and a melted vehicle onto a second solid carrier. Normally, the meltable vehicle has a melting point of at least 5°C, but the melting point is preferably below the melting point of tacrolimus. The melting point of the vehicle may be in the range of 10°C to 150°C.

[0110] An advantage of using the controlled agglomeration method described in WO 03/004001 is that it is possible to apply a relatively large amount of a melt to a particulate material without having an undesirable growth in particle size.

[0111] The solid solution may also be obtained e.g. by employing organic solvents or by dissolving the active substance in another suitable medium (e.g. an oil or an oily material that is in liquid form at room temperature or at elevated temperatures).

[0112] Solid dispersions (solvent method) are prepared by dissolving a physical mixture of the active substance (e.g. a drug substance) and the vehicle or carrier in a common organic solvent, followed by evaporation of the solvent. Suitable organic solvents include pharmaceutical acceptable solvent in which the active substance is soluble such as methanol, ethanol, methylene chloride, chloroform, ethylacetate, acetone or mixtures thereof.

[0113] Suitable water soluble carriers include polymers such as polyethylene glycol, poloxamers.

[0114] The solid dispersion is preferably formed by spray drying techniques, controlled agglomeration, freeze-drying or coating on carrier particles or any other solvent removal process. The dried product contains the active substance present in the form of a solid dispersion including a molecular dispersion and a solid solution.

[0115] As an alternative to the use of organic solvents the drug and polymer may be co-grinded or extruded at elevated temperatures (melt extrusion).

[0116] The pharmaceutical compositions comprising tacrolimus in form of a solid solution may in principle be prepared using any suitable procedure for preparing pharmaceutical compositions known within the art.

[0117] Apart from using the organic solvent based method, solid solutions of tacrolimus may be obtained by dissolving tacrolimus in the carrier composition used in the controlled agglomeration method. Stabilizing agents etc. may be added in order to ensure the stability of the solid dispersion/solution.

Uses

[0118] The solid solution of the invention or the pharmaceutical composition of the invention may be used in the preparation of an solid oral dosage form such as tablets, capsules or sachets; or for the preparation of granules, pellets microspheres or nanoparticles.

[0119] Preferably, the solid dispersion or solid solution is used in the preparation of an immediate release solid dosage form or a delayed release solid dosage form.

[0120] Other uses of the solid dispersion or solid solution of the invention is for the preparation of a topical dosage form.

[0121] A further advantage of a composition of the present invention is the possibility of obtaining an effective therapeutic response with a decreased dosage compared to traditional oral treatment. Thus it is contemplated that the solid dosage form of the invention, when orally administered to a mammal in need thereof in a dose that is at the most about 85% w/w such as, e.g., at the most about 80% w/w, at the most about 75%, at the most about 70% w/w, at the most about 65% w/w, at the most about 60% w/w, at the most about 55% w/w or at the most about 50% w/w of the dose of tacrolimus administered in the form of Prograf® or a similar commercially available tacrolimus-containing product, is essentially bioequivalent with Prograf® or a similar commercially available tacrolimus-containing product.

[0122] Any of the tacrolimus-containing dosage forms, compositions, dispersions or solutions of the invention may improved treatment of conditions that respond to tacrolimus treatment.

[0123] Tacrolimus is indicated (or has been suggested) for the treatment of diseases such as, e.g., rejection reactions by transplantation of organs or tissues such as the heart, kidney, liver, bone marrow, skin, cornea, lung, pancreas, small intestine, limb, muscle, nerve, intervertebral disc, trachea, myoblast, cartilage, etc.; graft-versus-host reactions following

bone marrow transplantation; autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes, etc.; infections caused by pathogenic microorganisms (e.g. *Aspergillus fumigatus*, *Fusarium oxysporum*, *Trichophyton asteroides*, etc.); inflammatory or hyperproliferative skin diseases or cutaneous manifestations of immunologically mediated diseases (e.g. psoriasis, atopic dermatitis, contact dermatitis, eczematoid dermatitis, seborrheic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, erythema, dermal eosinophilia, lupus erythematosus, acne, and alopecia areata); autoimmune diseases of the eye (e.g. keratoconjunctivitis, vernal conjunctivitis, uveitis associated with Behcet's disease, keratitis, herpetic keratitis, conical keratitis, corneal epithelial dystrophy, keratoleukoma, ocular pemphigus, Mooren's ulcer, scleritis, Graves' ophthalmopathy, Vogt-Koyanagi-Harada syndrome, keratoconjunctivitis sicca (dry eye), phlyctenule, iridocyclitis, sarcoidosis, endocrine ophthalmopathy, etc.); reversible obstructive airways diseases [asthma (e.g. bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, and dust asthma), particularly chronic or inveterate asthma (e.g. late asthma and airway hyper-responsiveness) bronchitis, etc.; mucosal or vascular inflammations (e.g. gastric ulcer, ischemic or thrombotic vascular injury, ischemic bowel diseases, enteritis, necrotizing enterocolitis, intestinal damages associated with thermal burns, leukotriene B₄-mediated diseases); intestinal inflammations/allergies (e.g. coeliac diseases, proctitis, eosinophilic gastroenteritis, mastocytosis, Crohn's disease and ulcerative colitis); food-related allergic diseases with symptomatic manifestation remote from the gastrointestinal tract (e.g. migraine, rhinitis and eczema); renal diseases (e.g. interstitial nephritis, Goodpasture's syndrome, hemolytic uremic syndrome, and diabetic nephropathy); nervous diseases (e.g. multiple myositis, Guillain-Barre syndrome, Meniere's disease, multiple neuritis, solitary neuritis, cerebral infarction, Alzheimer's diseases Parkinson's diseases, amyotrophic lateral sclerosis (ALS) and radiculopathy); cerebral ischemic disease (e.g., head injury, hemorrhage in brain (e.g., subarachnoid hemorrhage, intracerebral hemorrhage), cerebral thrombosis, cerebral embolism, cardiac arrest, stroke, transient ischemic attack (TIA), hypertensive encephalopathy, cerebral infarction); endocrine diseases (e.g. hyperthyroidism, and Basedow's disease); hematic diseases (e.g. pure red cell aplasia, aplastic anemia, hypoplastic anemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis, pernicious anemia, megaloblastic anemia, and anerythroplasia); bone diseases (e.g. osteoporosis); respiratory diseases (e.g. sarcoidosis, pulmonary fibrosis, and idiopathic interstitial pneumonia); skin diseases (e.g. dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris, photosensitivity, and cutaneous T-cell lymphoma); circulatory diseases (e.g. arteriosclerosis, atherosclerosis, aortitis syndrome, polyarteritis nodosa, and myocarditis); collagen diseases (e.g. scleroderma, Wegener's granuloma, and Sjogren's syndrome); adiposis; eosinophilic fasciitis; periodontal diseases (e.g. damage to gingiva, periodontium, alveolar bone or substantia ossea dentis); nephrotic syndrome (e.g. glomerulonephritis); male pattern alopecia, alopecia senile; muscular dystrophy; pyoderma and Sezary syndrome; chromosome abnormality-associated diseases (e.g. Down's syndrome); Addison's disease; active oxygen-mediated diseases [e.g. organ injury (e.g. ischemic circulation disorders of organs (e.g. heart, liver, kidney, digestive tract, etc.) associated with preservation, transplantation, or ischemic diseases (e.g. thrombosis, cardiac infarction, etc.)); intestinal diseases (e.g. endotoxin shock, pseudomembranous colitis, and drug- or radiation-induced colitis); renal diseases (e.g. ischemic acute renal insufficiency, chronic renal failure); pulmonary diseases (e.g. toxicosis caused by pulmonary oxygen or drugs (e.g. paracort, bleomycin, etc.), lung cancer, and pulmonary emphysema); ocular diseases (e.g. cataracta, iron-storage disease (siderosis bulbi), retinitis, pigmentosa, senile plaques, vitreous scarring, corneal alkali burn); dermatitis (e.g. erythema multiforme, linear immunoglobulin A bullous dermatitis, cement dermatitis); and other diseases (e.g. gingivitis, periodontitis, sepsis, pancreatitis, and diseases caused by environmental pollution (e.g. air pollution), aging, carcinogen, metastasis of carcinoma, and hypobaropathy)]; diseases caused by histamine release or leukotriene C₄ release; restenosis of coronary artery following angioplasty and prevention of postsurgical adhesions; autoimmune diseases and inflammatory conditions (e.g., primary mucosal edema, autoimmune atrophic gastritis, premature menopause, male sterility, juvenile diabetes mellitus, pemphigus vulgaris, pemphigoid, sympathetic ophthalmitis, lens-induced uveitis, idiopathic leukopenia, active chronic hepatitis, idiopathic cirrhosis, discoid lupus erythematosus, autoimmune orchitis, arthritis (e.g. arthritis deformans), or polychondritis); Human Immunodeficiency Virus (HIV) infection, AIDS; allergic conjunctivitis; hypertrophic cicatrix and keloid due to trauma, burn, or surgery.

[0124] In addition, tricyclic macrolides like e.g. tacrolimus have liver regenerating activity and/or activities of stimulating hypertrophy and hyperplasia of hepatocytes. Therefore, the pharmaceutical composition of the present invention is useful for increasing the effect of the therapy and/or prophylaxis of liver diseases [e.g. immunogenic diseases (e.g. chronic autoimmune liver diseases such as autoimmune hepatic diseases, primary biliary cirrhosis or sclerosing cholangitis), partial liver resection, acute liver necrosis (e.g. necrosis caused by toxins, viral hepatitis, shock, or anoxia), hepatitis B, non-A non-B hepatitis, hepatocirrhosis, and hepatic failure (e.g. fulminant hepatitis, late-onset hepatitis and "acute-on-chronic" liver failure (acute liver failure on chronic liver diseases))].

[0125] Furthermore, a composition of the present invention is useful for increasing the effect of the prevention and/or treatment of various diseases because of the useful pharmacological activity of the tricyclic macrolides, such as augmenting activity of chemotherapeutic effect, activity of cytomegalovirus infection, anti-inflammatory activity, inhibiting activity against peptidyl-prolyl isomerase or rotamase, antimalarial activity, antitumor activity and so on.

*Materials and methods**Materials*

- 5 **[0126]** Tacrolimus (supplied by Eurotrade); batch no RD 03-111
 Lactose monohydrate 200 mesh (from DMV)
 Granulated silicium oxide, Aeroperl® 300, (Degussa)
 Polyethylene glycol 6000, Pluracol® E6000 (from BASF)
 Poloxamer 188, Pluronic® F-68 (from BASF)
- 10 Glyceryl monostearate, Rylo® MD50, (from Danisco Cultor), grade Ph. Eur.; batch no. 4010056276
 Avicel PH200 (microcrystalline cellulose) (from FMC)
 Lactose DCL 11 (from DMV)
 Magnesium stearate
 Croscarmellose sodium, Ac-Di-Sol® (from FMC)
- 15 Eudragit® L30D.55 (from Degussa); batch no. 1220314079
 Triethyl citrate (from Merck); batch no. RD03-122
 Anti-foam emulsion (from Unikem)
 Micro talc
- 20 **[0127]** Either tablets, capsules or granules might be enteric coated with different types of polymers such as hydroxypropylmethylcellulose acetate succinate (Aqoat), cellulose acetate phthalate CAP, hydroxypropylmethylcellulose phthalate HPMCP or methacrylic acid copolymers such as Eudragit L30D, Eudragit 100/S, Eudragit 100/L.
- [0128]** Comparison prior art tacrolimus formulation for in vivo studies:

Prograf® Hard Gelatin Capsules, manufactured by Fujisawa Ireland Ltd.

25	<i>Ingredients</i>	mg	
	Tacrolimus, anhydr.	1.0	
	Gelatin	6.9	
	Hypromellose	1.0	
30	Lactose monohydrate	24.7	
	Magnesium stearate	0.3	
	Shellac		q.s.
	Soybean lecithine	q.s.	
	Iron oxide red (E172)	q.s.	
35	Titanium dioxide (E171)	q.s.	
	Dimeticone (E900)	q.s.	

Methods

40 Determination of weight variation

[0129] The tablets prepared in the Examples herein were subjected to a test for weight variation performed in accordance with Ph. Eur.

45 Determination of average tablet hardness

[0130] The tablets prepared in the Examples herein were subjected to a test for tablet hardness employing Schleuniger Model 6D apparatus and performed in accordance with the general instructions for the apparatus.

50 Determination of disintegration time

[0131] The time for a tablet to disintegrate, i.e. to decompose into particles or agglomerates, was determined in accordance with Ph. Eur.

55 Determination of geometric weight mean diameter d_{gw}

[0132] The geometric weight mean diameter was determined by employment of a method of laser diffraction dispersing

the particulate material obtained (or the starting material) in air. The measurements were performed at 1 bar dispersive pressure in Sympatec Helos equipment, which records the distribution of the equivalent spherical diameter. This distribution is fitted to a log normal volume-size distribution.

[0133] When used herein, "geometric weight mean diameter" means the mean diameter of the log normal volume-size distribution.

In vitro dissolution tests

[0134] The following test methods were applied to the compositions and dosage forms of the present invention.

Test 1:

[0135] In vitro dissolution test according to USP Method A, delayed release articles (USP paddle method; rotation speed: 50 rpm; 37°C; after 2 hours in acidic medium, the medium is changed to phosphate buffer pH 6.8.).

Test 2:

[0136] In vitro dissolution test in aqueous dissolution medium adjusted to pH 4.5 (900 ml water with 0.005% HPC (hydroxypropylcellulose) adjusted to pH 4.5; 37°C; USP Paddle method; rotation speed: 50 rpm).

In vivo studies in Beagle dogs

[0137] In vivo studies with the purpose of determining the bioavailability of the compositions of the present invention relative to the bioavailability of the commercially available tacrolimus product, i.e. Prograf^(R), was performed using Beagle dogs.

[0138] The experimental work was performed in Denmark using male Beagle dogs each having a body weight of 12-18 kg (starting weight). The studies were conducted as open, non-randomised, cross-over studies. The dogs were premedicated with Primperan inj. 5mg/ml (anti-emetic) and an oral dose of 0.5 to 4 mg of tacrolimus was administered.

[0139] The dogs were fasted for 10 hours prior to dosing (water ad libitum) and were fed 5 hours after dosing (water ad libitum). Each dog was dosed with the specified dose of tacrolimus without taking the weight of the dog into consideration.

[0140] Blood samples were collected at vena jugularis externa at the following points of time: Pre-dose, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours after dosing. 4 ml of blood were collected, mixed with EDTA, and the samples were frozen (-80°C). The blood samples were analyzed using on-line extraction LC/MS and results were given in ng/mL.

[0141] The determined full blood concentration profiles of tacrolimus were treated using the Pharmacokinetic software WinNonlin[®], (Pharsight, California; USA) to calculate the pharmacokinetic parameters. All data are dose adjusted.

[0142] The following examples serve the purpose of illustration of the invention and are not intended to limit the scope of the present invention.

[0143] Pharmaceutical compositions and dosage forms of the invention are exemplified in examples 1-4 including results of in vitro dissolution tests. Results of in vivo comparison studies in Beagle dogs (blood plasma concentration) are found in examples 5-6.

EXAMPLE 1

[0144] Immediate release tablet with improved bioavailability

Tablet composition:

	%	mg
Tacrolimus	0.50	1.00
Lactose 200 mesh	49.75	100.00
PEG 6000	34.48	69.30
Poloxamer 188	14.78	29.70
Magnesium stearate	0.50	1.01
Total	100.00	201.01

[0145] Tacrolimus was dissolved in polyethylene glycol 6000 and poloxamer 188 (in a 70:30 w/w ratio) at 70°C. The

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solution was sprayed onto 250 g lactose in a fluid bed Strea-1. The granular product was sifted through sieve no. 0.7 mm and blended with magnesium stearate for 0.5 minutes in a Turbula mixer. The mixture was compressed into 8 mm tablets of 1 mg active ingredient (200 mg tablet) with compound cup shaped.

[0146] Mean disintegration time: 20 minutes. Hardness: 45 N.

EXAMPLE 2

[0147] Immediate release tablet based on PEG 6000/Poloxamer 188

Tablet composition:

Substance	%	mg
Tacrolimus	1.98	2.00
Lactose monohydrate, Lactose 200 mesh	40.50	40.91
PEG 6000	33.26	33.60
Poloxamer 188, Lutrol 68	14.40	14.40
Magnesium Stearate	0.50	0.51
Talc	4.50	4.55
Croscarmellose sodium, Ac-Di-Sol	5.00	5.05
	100.00	101.01

[0148] Tacrolimus was dissolved in PEG 6000 at a temperature above 80°C. Poloxamer 188 was added and the solution was heated to a temperature above 80°C. Using feed unit Phast FS1.7, the solution was sprayed onto 200 g lactose monohydrate in a fluid bed Phast FB100. The resulting granulate was passed through a Comill, sieve no. 1397, 4500rpm, and blended with croscarmellose sodium for 3 minutes in a Turbula mixer.

[0149] Magnesium stearate and talc was sifted through sieve no. 300 and mixed in a Turbula mixer for 3 min. The granulate was mixed with the magnesium stearate:talc (1:9) for 0.5 minutes in a Turbula mixer.

[0150] The resulting mixture was compressed into 6 mm tablets of 2 mg active ingredient (100 mg tablet) with compound cup shape.

[0151] Mean disintegration time: 7 minutes. Hardness: 65 N

[0152] The tablets were subjected to an in vitro dissolution test in dissolution medium: 900 ml, aqueous medium with 0.005% HPC (hydroxypropylcellulose) adjusted to pH = 4.5, USP paddle method; rotation speed: 50 rpm; and the following dissolution profile was found:

Time (minutes)	% release	Rsd %
0	0	0
5	27.2	15.1
10	49.1	10.9
20	80.7	8.0
35	98.9	5.4
42	102.7	3.6
52	104.9	2.0

EXAMPLE 3

Enteric coating of immediate release tablets of example 2

[0153] The enteric coating is based on the acrylic polymer Eudragit L30D-55. Eudragit L30D is supplied as an aqueous latex suspension creating a water insoluble film when the water is evaporated during coating. The polymer is insoluble at pH-values below 5.0 and readily soluble at pH-values above 6.0. The tablets prepared as described in example 2

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were coated with the following film coating composition:

Substance	w/w%
Eudragit L30D-55	40
Water	52
Triethyl citrate	1.8
Anti-foam emulsion	0.2
Talc (micro)	6
Total	100

The amount of applied film polymer (Eudragit) is based on a calculation of mg filmpolymer per cm² of tablet surface. The thickness of the enteric coating was 80 μm. A verification of the film-thickness applied was based on measuring the increase in tablet height with a digital micrometer. The film coating process was performed in a Phast FB100 fluid bed equipped with a Wurster like insert using an inlet air temperature of 50°C, inlet air flow of 100 cbm per hour, product temperature of 38°C and feed rate 15 g/min.

[0154] The coated tablets were cured in an oven at 30°C for 48 hours. Alternatively, the coated tablets may more efficiently be cured at 40°C for 24 hours.

[0155] The enteric coated tablets were subjected to in vitro dissolution tests using two different dissolution media/tests.

[0156] Using the dissolution medium/test: 900 ml aqueous medium with 0.005% HPC (hydroxypropylcellulose) adjusted to pH = 4.5 (USP paddle method; rotation speed: 50 rpm), the following dissolution profile was found:

Time (hours)	% release	Rsd %
0	0	0
4	0.8	32.3
8	0.4	61.1
15	11.0	17.3
17	13.2	12.1

[0157] Using the dissolution medium/test: USP Method A, delayed release articles (USP paddle method; rotation speed: 50 rpm), the following dissolution profile was found:

Time (minutes)	% release	Rsd %
0	0	NA
120	0	NA
155	84.8	12.8
165	102.9	NA
175	101.0	3.5

EXAMPLE 4

[0158] The following tacrolimus formulation was prepared as described in example 2:

Substance	%	mg
Tacrolimus	2.09	2.10
Lactose monohydrate, 200 mesh	42.75	42.95
PEG 6000	35.11	35.28

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(continued)

Substance	%	mg
Poloxamer 188, Lutrol 68	15.05	15.12
Magnesium stearate	0.50	0.50
Talc	4.50	4.52
	100.00	100.48

The mixture was compressed into 6 mm tablets of 2.1 mg active ingredient (100 mg tablet with compound cup shape). Average tablet hardness: 41 N.

EXAMPLE 5

In vivo test of immediate release formulations in dogs

[0159] The following tacrolimus formulation was prepared as described in example 2:

Substance	%	mg
Tacrolimus	0.76	0.5
Lactose 200 mesh	49.14	32.43
PEG 6000	34.73	22.92
Poloxamer 188	14.88	9.82
magnesium stearate	0.50	0.33
Total	100.00	66.00

66 mg of the granulate was weighed into hard gelatine capsules.

[0160] An in vivo study of this formulation 0.5 mg in a Beagle dog, performed as described above under Methods, relative to Prograf®, 4 x 1 mg (Batch no.: 1 C56050), gave the following results:

Blood concentrations (ng/mL) in dog no. F1182, after administration of formulation:

Time (hr)	Formulation	
	Prograf (4 mg)	Invention Dose adj. to 4 mg
0	0	0.0
0.5	0.5	10.5
1.0	5.5	44.1
1.5	4.1	34.3
2.0	4.0	21.0
3.0	4.6	10.5
4.0	4.0	9.1
6.0	2.7	4.9
8.0	2.0	4.2
12.0	2.0	3.5
24.0	0.7	2.1

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Relative bioavailability based on AUC (invention/Prograf): 293%.

EXAMPLE 6

In vivo test of immediate release formulations in dogs

[0161] The following tacrolimus formulation of the invention was prepared as described in example 2:

Substance	%	mg
Tacrolimus	1.86	0.50
Lactose monohydrate, Lactose 200 mesh	43.56	11.72
PEG 6000	31.21	8.40
Poloxamer 188, Lutrol 68	13.37	3.60
Magnesium Stearate	0.50	0.13
Talc	4.50	1.21
Croscarmellose sodium, Ac-Di-Sol	5.00	1.35
	100.00	26.92

[0162] This was compressed into 4 mm tablets of 0.5 mg active ingredient (27 mg tablet with compound cup shape).

[0163] An in vivo study of this formulation 0.5 mg in a Beagle dog, performed as described above under Methods, relative to Prograf®, 0.5 mg capsules (Batch no.: OC512OD), gave the following results: Blood concentrations (ng/mL) in dog no. 1, after administration of formulation:

Time (hr)	Formulation	
	Prograf (0.5 mg)	Formulation B (0.5 mg)
0	0	0
0.5	0.95	0.04
1.0	0.84	1.56
1.5	0.55	4.68
2.0	0.40	9.11
3.0	0.26	2.82
4.0	0.18	2.46
6.0	0.18	1.10
8.0	0.14	1.25
12.0	0.11	0.74
24.0	0.06	0.40
25.0	0.06	0.44

Relative bioavailability based on AUC (invention vs. Prograf): 742%.

Claims

1. A pharmaceutical composition comprising a solid solution of tacrolimus dissolved in a hydrophilic or water miscible vehicle, wherein the vehicle is a mixture of polyethylene glycol and poloxamer in a proportion of between 1:3 and 10:1, wherein the melting point of the vehicle is at least 20°C and wherein tacrolimus is present therein in a concentration of between about 0.01 w/w% and about 15 w/w% to form a solid solution at ambient temperature.

2. The composition according to claim 1, wherein the concentration of tacrolimus in polyethylene glycol and poloxamer is at the most 10 w/w%.
- 5 3. The composition according to claim 1, wherein the concentration of tacrolimus in polyethylene glycol and poloxamer is at least about 0.05 w/w%.
4. The pharmaceutical composition according to claim 1, wherein at least 50 w/w% of tacrolimus is released within about 30 minutes, when tested in any dissolution test according to USP using an aqueous dissolution medium.
- 10 5. The pharmaceutical composition according to claim 1, wherein at least 75 w/w% of tacrolimus is released within about 40 minutes, when tested in any dissolution test according to USP using an aqueous dissolution medium.
6. The pharmaceutical composition according to claim 1, wherein at least 90 w/w% of tacrolimus is released within about 60 minutes, when tested in any dissolution test according to USP using an aqueous dissolution medium.
- 15 7. The pharmaceutical composition according to claim 1, wherein the polyethylene glycol has an average molecular weight of at least 1500.
8. The pharmaceutical composition according to claim 1, wherein polyethylene glycol and poloxamer is present in a proportion of between 1:1 and 5:1, preferably between 3:2 and 4:1, more preferably between 2:1 and 3:1, in particular about 7:3.
- 20 9. The pharmaceutical composition according to claim 1, wherein the poloxamer is poloxamer 188.
- 25 10. The pharmaceutical composition according to claim 1, wherein the polyethylene glycol has an average molecular weight of about 6000 (PEG6000).
11. The pharmaceutical composition according to any claim 1 to 10 further comprising one or more pharmaceutically acceptable excipients.
- 30 12. The pharmaceutical composition according to claim 11, wherein the pharmaceutically acceptable excipients are selected from the group consisting of fillers, disintegrants, binders and lubricants.
13. The pharmaceutical composition according to claim 11 in particulate form, for example in powder form.
- 35 14. The pharmaceutical composition according to claim 13, wherein the particles have a geometric weight mean diameter d_{gw} from about 10 μm to about 2000 μm , preferably from about 20 μm to about 2000 μm , especially from about 50 μm to about 300 μm .
- 40 15. The pharmaceutical composition according to claim 13, wherein the particles have a geometric weight mean diameter d_{gw} from about 50 μm to about 300 μm .
16. A dosage form comprising the pharmaceutical composition according to claim 11, which is a solid oral dosage form.
- 45 17. The dosage form according to claim 16, which is a unit dosage form.
18. The dosage form according to claim 16, which further comprises a pharmaceutically acceptable additive selected from the group consisting of flavoring agents, coloring agents, taste-masking agents, pH-adjusting agents, buffering agents, preservatives, stabilizing agents, anti-oxidants, wetting agents, humidity-adjusting agents, surface-active agents, suspending agents, absorption enhancing agents and release modifying agents.
- 50 19. The dosage form according to claim 16, wherein at least one pharmaceutically acceptable excipient is selected from the group consisting of silica acid or a derivative or salt thereof including silicates, silicon dioxide and polymers thereof; magnesium aluminosilicate and/or magnesium aluminometasilicate, bentonite, kaolin, magnesium trisilicate, montmorillonite and/or saponite.
- 55 20. The dosage form according to claim 16, wherein at least one pharmaceutically acceptable excipient is a silica acid or a derivative or salt thereof.

21. The dosage form according to claim 16, wherein at least one pharmaceutically acceptable excipient is silicon dioxide or a polymer thereof.
22. The dosage form according to claim 18 comprising one or more release modifying agents selected from the group consisting of water-miscible polymers, water-insoluble polymers, oils and oily materials.
23. The dosage form according to claim 22, wherein the water-insoluble polymer is selected from the group consisting of ethyl cellulose, cellulose acetate, cellulose nitrate, and mixtures thereof.
24. The dosage form according to claim 22, wherein the oil or oily material is selected from the group consisting of hydrophilic and hydrophobic oils or oily materials.
25. The dosage form according to claim 22, wherein the oil or oily material is hydrophilic and selected from the group consisting of polyether glycols such as polypropylene glycols; polyoxyethylenes; polyoxypropylenes; poloxamers; polyglycolized glycerides and mixtures thereof.
26. The dosage form according to claim 22, wherein the oil or oily material is hydrophobic and selected from the group consisting of straight chain saturated hydrocarbons, sorbitan esters, paraffins; fats and oils such as cacao butter, beef tallow, lard, polyether glycol esters; higher fatty acid such as stearic acid, myristic acid, palmitic acid, higher alcohols such as cetanol, stearyl alcohol, low melting point waxes such as glyceryl monostearate, glyceryl monooleate, hydrogenated tallow, myristyl alcohol, stearyl alcohol, substituted and/or unsubstituted monoglycerides, substituted and/or unsubstituted diglycerides, substituted and/or unsubstituted triglycerides, yellow beeswax, white beeswax, carnauba wax, castor wax, japan wax, acetylate monoglycerides; NVP polymers, PVP polymers, acrylic polymers, and mixtures thereof.
27. The dosage form according to claim 26, wherein the oil or oily hydrophobic material has a melting point of at least about 20°C.
28. The dosage form according to claim 22, wherein the water-miscible polymer is a cellulose derivative selected from the group consisting of hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), methylcellulose, sodium carboxymethylcellulose, hydroxyethyl cellulose, poloxamers, polyoxyethylene stearates, poly-ε-caprolactone, polyvinylpyrrolidone (PVP), polyvinylpyrrolidone-polyvinylacetate copolymer PVP-PVA, polymethacrylic polymers and polyvinyl alcohol (PVA), poly(ethylene oxide) (PEO) and mixtures thereof.
29. The dosage form according to claim 22, which is entero-coated using a water-miscible polymer having a pH-dependent solubility in water.
30. The dosage form according to claim 29, wherein the water-miscible polymer is selected from the group consisting of polyacrylamides; phthalate derivatives such as acid phthalates of carbohydrates including amylose acetate phthalate, cellulose acetate phthalate, cellulose acetate terephthalate, cellulose acetate isophthalate, other cellulose ester phthalates, cellulose ether phthalates, hydroxypropyl cellulose phthalate, hydroxypropylcellulose acetate phthalate, hydroxypropyl ethylcellulose phthalate, hydroxypropyl methylcellulose phthalate (HMPCP), methylcellulose phthalate, methyl cellulose acetate phthalate, polyvinyl acetate phthalate, polyvinyl acetate hydrogen phthalate, sodium cellulose acetate phthalate, starch acid phthalate; phthalates of other compounds including polyvinyl acetate phthalate (PVAP); other cellulose derivatives including hydroxypropyl methylcellulose acetate succinate (HPMCAS), carboxymethylcellulose, cellulose acetate trimellitate; alginates; carbomers; polyacrylic acid derivatives such as acrylic acid and acrylic ester copolymers, polymethacrylic acid and esters thereof, poly acrylic methacrylic acid copolymers, methacrylic acid copolymers; styrene-maleic acid dibutyl phthalate copolymer, styrene-maleic acid polyvinylacetate phthalate copolymer, styrene and maleic acid copolymers; shellac, starch glycolate; polacrylin; vinyl acetate and crotonic acid copolymers and mixtures thereof.
31. The dosage form according to claim 29, which upon oral administration to a mammal in need thereof releases at the most about 10 w/w%, preferably at the most about 7.5 w/w%, more preferably at the most about 5 w/w%, especially at the most about 2 w/w% of the total amount of active ingredient within the first 3 hours, preferably within 2 hours, more preferably within 1 hours, in particular within about 30 minutes after administration..
32. The solid dosage form according to claim 16, wherein the solid dosage form upon oral administration to a mammal

in need thereof releases at least 50% w/w of the active ingredient within 24 hours, preferably within 20 hours, more preferably within 18 hours, especially within 15 hours, in particular within 12 hours.

33. Use of the composition according to claim 1 for the preparation of a solid oral dosage form such as tablets, capsules or sachets.
34. Use of the composition according to claim 1 for the preparation of granules, pellets, microspheres or nanoparticles.
35. Use of the composition according to claim 1 for the preparation of an immediate release solid dosage form.
36. Use of the composition according to claim 1 for the preparation of a delayed release solid dosage form.
37. Use of the composition according to claim 1 for the preparation of a topical dosage form.
38. The dosage form according to claim 16 for use in the treatment of conditions that respond to tacrolimus treatment.
39. The dosage form according to claim 38 for use in the treatment of rejection reactions by transplantation of organs or tissues or treatment of autoimmune disease.
40. The dosage form according to claim 16 for use in the treatment of a patient in need thereof with a once daily dosage of tacrolimus of from 0.02 mg/kg/day to 0.15mg/kg/day.
41. A method for the preparation of the composition according to claim 1, the method comprising the step of dissolving tacrolimus in polyethylene glycol and poloxamer to obtain a solid solution at ambient temperature.

Patentansprüche

1. Pharmazeutische Zusammensetzung umfassend eine feste Lösung von Tacrolimus gelöst in einem hydrophilen oder mit Wasser mischbaren Vehikel, wobei das Vehikel eine Mischung aus Polyethylenglycol und Poloxamer in einem Verhältnis zwischen 1:3 und 10:1 ist, wobei der Schmelzpunkt des Vehikels wenigstens 20°C beträgt und wobei Tacrolimus darin in einer Konzentration zwischen ungefähr 0,01 Gew./Gew.-% und ungefähr 15 Gew./Gew.-% vorhanden ist, um eine feste Lösung bei Umgebungstemperatur zu bilden.
2. Zusammensetzung nach Anspruch 1, wobei die Konzentration von Tacrolimus in Polyethylenglycol und Poloxamer höchstens 10 Gew./Gew.-% beträgt.
3. Zusammensetzung nach Anspruch 1, wobei die Konzentration von Tacrolimus in Polyethylenglycol und Poloxamer wenigstens ungefähr 0,05 Gew./Gew.-% beträgt.
4. Pharmazeutische Zusammensetzung nach Anspruch 1, wobei wenigstens 50 Gew./Gew.-% Tacrolimus innerhalb von ungefähr 30 Minuten freigesetzt wird, wenn in einem beliebigen Auflösungstest gemäß USP unter Verwendung eines wässrigen Auflösungsmediums getestet wird.
5. Pharmazeutische Zusammensetzung nach Anspruch 1, wobei wenigstens 75 Gew./Gew.-% Tacrolimus innerhalb von ungefähr 40 Minuten freigesetzt wird, wenn in einem beliebigen Auflösungstest gemäß USP unter Verwendung eines wässrigen Auflösungsmediums getestet wird.
6. Pharmazeutische Zusammensetzung nach Anspruch 1, wobei wenigstens 90 Gew./Gew.-% Tacrolimus innerhalb von ungefähr 60 Minuten freigesetzt wird, wenn in einem beliebigen Auflösungstest gemäß USP unter Verwendung eines wässrigen Auflösungsmediums getestet wird.
7. Pharmazeutische Zusammensetzung nach Anspruch 1, wobei das Polyethylenglycol ein mittleres Molekulargewicht von wenigstens 1500 aufweist.
8. Pharmazeutische Zusammensetzung nach Anspruch 1, wobei Polyethylenglycol und Poloxamer in einem Verhältnis zwischen 1:1 und 5:1, vorzugsweise zwischen 3:2 und 4:1, mehr bevorzugt zwischen 2:1 und 3:1, insbesondere in einem Verhältnis von ungefähr 7:3 vorhanden sind.

9. Pharmazeutische Zusammensetzung nach Anspruch 1, wobei das Poloxamer Poloxamer 188 ist.
10. Pharmazeutische Zusammensetzung nach Anspruch 1, wobei das Polyethylenglycol ein mittleres Molekulargewicht von ungefähr 6000 aufweist (PEG6000).
11. Pharmazeutische Zusammensetzung nach einem der Ansprüche 1 bis 10, außerdem umfassend einen oder mehrere pharmazeutisch verträgliche Exzipienten.
12. Pharmazeutische Zusammensetzung nach Anspruch 11, wobei die pharmazeutisch verträglichen Exzipienten ausgewählt sind aus der Gruppe bestehend aus Füllstoffen, Sprengmitteln, Bindemitteln und Schmiermitteln.
13. Pharmazeutische Zusammensetzung nach Anspruch 11 in partikulärer Form, z.B. in Pulverform.
14. Pharmazeutische Zusammensetzung nach Anspruch 13, wobei die Partikel einen geometrisch gewichteten mittleren Durchmesser (geometric weight mean diameter) d_{gw} von ungefähr 10 μm bis ungefähr 2000 μm , vorzugsweise von ungefähr 20 μm bis ungefähr 2000 μm , insbesondere von ungefähr 50 μm bis ungefähr 300 μm aufweisen.
15. Pharmazeutische Zusammensetzung nach Anspruch 13, wobei die Partikel einen geometrisch gewichteten mittleren Durchmesser d_{gw} von ungefähr 50 μm bis ungefähr 300 μm aufweisen.
16. Dosierungsform umfassend eine pharmazeutische Zusammensetzung nach Anspruch 11, welche eine feste orale Dosierungsform ist.
17. Dosierungsform nach Anspruch 16, welche eine Einheitsdosierungsform ist.
18. Dosierungsform nach Anspruch 16, welche außerdem ein pharmazeutisch verträgliches Additiv umfasst, das ausgewählt ist aus der Gruppe bestehend aus Aromastoffen, Färbemitteln, Geschmacksmaskierungsmitteln, Mitteln zum Einstellen des pH, Puffersubstanzen, Konservierungsmitteln, Stabilisierungsmitteln, Antioxidantien, Netzmitteln, Mitteln zum Einstellen der Feuchtigkeit, oberflächenaktiven Stoffen, Suspendiermitteln, absorptionsverbessernden Mitteln und die Freisetzung modifizierenden Mitteln.
19. Dosierungsform nach Anspruch 16, wobei wenigstens ein pharmazeutisch verträglicher Exzipient ausgewählt ist aus der Gruppe bestehend aus Kieselsäure oder einem Derivat oder Salz davon, einschließlich Silicate, Siliciumdioxid und Polymere davon; Magnesiumaluminiumsilicat und/oder Magnesiumaluminiummetasilicat, Bentonit, Kaolin, Magnesiumtrisilicat, Montmorillonit und/oder Saponit.
20. Dosierungsform nach Anspruch 16, wobei wenigstens ein pharmazeutisch verträglicher Exzipient eine Kieselsäure oder ein Derivat oder Salz davon ist.
21. Dosierungsform nach Anspruch 16, wobei wenigstens ein pharmazeutisch verträglicher Exzipient Siliciumdioxid oder ein Polymer davon ist.
22. Dosierungsform nach Anspruch 18, umfassend ein oder mehrere die Freisetzung modifizierende Mittel ausgewählt aus der Gruppe bestehend aus mit Wasser mischbaren Polymeren, wasserunlöslichen Polymeren, Ölen und öligen Materialien.
23. Dosierungsform nach Anspruch 22, wobei das wasserunlösliche Polymer ausgewählt ist aus der Gruppe bestehend aus Ethylcellulose, Celluloseacetat, Cellulosenitrat und Mischungen davon.
24. Dosierungsform nach Anspruch 22, wobei das Öl oder ölige Material ausgewählt ist aus der Gruppe bestehend aus hydrophilen und hydrophoben Ölen oder öligen Materialien.
25. Dosierungsform nach Anspruch 22, wobei das Öl oder ölige Material hydrophil ist und ausgewählt ist aus der Gruppe bestehend aus Polyetherglycolen, wie Polypropylenglycolen; Polyoxyethylenen; Polyoxypropylenen; Poloxameren; polyglycolisierten Glyceriden und Mischungen davon.
26. Dosierungsform nach Anspruch 22, wobei das Öl oder ölige Material hydrophob ist und ausgewählt ist aus der Gruppe bestehend aus geradkettigen gesättigten Kohlenwasserstoffen, Sorbitanestern, Paraffinen; Fetten und Ölen,

wie Kakaobutter, Rindertalg, Schmalz, Polyetherglycolester; einer höheren Fettsäure, wie Stearinsäure, Myristinsäure, Palmitinsäure, höheren Alkoholen, wie Cetanol, Stearylalkohol, Wachsen mit niedrigem Schmelzpunkt, wie Glycerylmonosterarat, Glycerylmonooleat, hydriertem Talg, Myristylalkohol, Stearylalkohol, substituierten und/oder unsubstituierten Monoglyceriden, substituierten und/oder unsubstituierten Diglyceriden, substituierten und/oder unsubstituierten Triglyceriden, gelbem Bienenwachs, weißem Bienenwachs, Carnaubawachs, Rizinuswachs, Japanwachs, Acetylmonoglyceriden; NVP-Polymeren, PVP-Polymeren, Acrylpolymeren und Mischungen davon.

27. Dosierungsform nach Anspruch 26, wobei das Öl oder ölige hydrophobe Material einen Schmelzpunkt von wenigstens ungefähr 20°C aufweist.

28. Dosierungsform nach Anspruch 22, wobei das mit Wasser mischbare Polymer ein Cellulosederivat ist, das ausgewählt ist aus der Gruppe bestehend aus Hydroxypropylmethylcellulose (HPMC), Hydroxypropylcellulose (HPC), Methylcellulose, Natriumcarboxymethylcellulose, Hydroxyethylcellulose, Poloxameren, Polyoxyethylen-stearaten, Poly-ε-caprolacton, Polyvinylpyrrolidon (PVP), Polyvinylpyrrolidon-Polyvinylacetat-Copolymer PVP-PVA, Polymethacrylpolymeren und Polyvinylalkohol (PVA), Poly(ethylenoxid) (PEO) und Mischungen davon.

29. Dosierungsform nach Anspruch 22, welche unter Verwendung eines mit Wasser mischbaren Polymers mit einer pH-abhängigen Löslichkeit in Wasser magensaftresistent überzogen ist.

30. Dosierungsform nach Anspruch 29, wobei das mit Wasser mischbare Polymer ausgewählt ist aus der Gruppe bestehend aus Polyacrylamiden; Phthalatderivaten wie Säurephthalaten von Kohlehydraten einschließlich Amyloseacetatphthalat, Celluloseacetatphthalat, Celluloseacetaterephthalat, Celluloseacetatisophthalat, anderen Celluloseesterphthalaten, Celluloseetherphthalaten, Hydroxypropylcellulosephthalat, Hydroxypropylcelluloseacetatphthalat, Hydroxypropylethylcellulosephthalat, Hydroxypropylmethylcellulosephthalat (HMPCP), Methylcellulosephthalat, Methylcelluloseacetatphthalat, Polyvinylacetatphthalat, Polyvinylacetathydrogenphthalat, Natriumcelluloseacetatphthalat, Stärkesäurephthalat; Phthalaten von anderen Verbindungen, einschließlich Polyvinylacetatphthalat (PVAP); anderen Cellulosederivaten einschließlich Hydroxypropylmethylcelluloseacetatsuccinat (HPMCAS), Carboxymethylcellulose, Celluloseacetatrimellitat; Alginaten, Carbomeren; Polyacrylsäurederivaten, wie Acrylsäure und Acrylester-Copolymeren, Polymethacrylsäure und Estern davon, Polyacryl-Methacrylsäure-Copolymeren, Methacrylsäure-Copolymeren; Styrol-Maleinsäure-Dibutylphthalat-Copolymer, Styrol-Maleinsäure-Polyvinylacetat-Phthalat-Copolymer, Styrol- und Maleinsäure-Copolymeren; Schellack, Stärkelycolat; Polacrylin; Vinylacetat und Crotonsäurecopolymeren und Mischungen davon.

31. Dosierungsform nach Anspruch 29, welche nach einer oralen Verabreichung an einen Säuger, der dies benötigt, höchstens ungefähr 10 Gew./Gew.-%, vorzugsweise höchstens ungefähr 7,5 Gew./Gew.-%, mehr bevorzugt höchstens ungefähr 5 Gew./Gew.-%, insbesondere höchstens ungefähr 2 Gew./Gew.-% der gesamten Menge an Wirkstoff innerhalb der ersten 3 Stunden, vorzugsweise innerhalb von 2 Stunden, mehr bevorzugt innerhalb von 1 Stunde, insbesondere innerhalb von ungefähr 30 Minuten nach der Verabreichung freisetzt.

32. Feste Dosierungsform nach Anspruch 16, wobei die feste Dosierungsform nach einer oralen Verabreichung an einen Säuger, der dies benötigt, wenigstens 50 % Gew./Gew. des Wirkstoffs innerhalb von 24 Stunden, vorzugsweise innerhalb von 20 Stunden, mehr bevorzugt innerhalb von 18 Stunden, besonders innerhalb von 15 Stunden, insbesondere innerhalb von 12 Stunden freisetzt.

33. Verwendung der Zusammensetzung nach Anspruch 1 für die Herstellung einer festen oralen Dosierungsform, wie Tabletten, Kapseln oder Sachets.

34. Verwendung der Zusammensetzung nach Anspruch 1 für die Herstellung von Körnchen, Pellets, Mikrokugeln oder Nanopartikeln.

35. Verwendung der Zusammensetzung nach Anspruch 1 für die Herstellung einer festen Dosierungsform mit sofortiger Freisetzung.

36. Verwendung der Zusammensetzung nach Anspruch 1 für die Herstellung einer festen Dosierungsform mit verzögerter Freisetzung.

37. Verwendung der Zusammensetzung nach Anspruch 1 für die Herstellung einer topischen Dosierungsform.

38. Dosierungsform nach Anspruch 16 zur Verwendung bei der Behandlung von Zuständen, welche auf eine Tacrolimusbehandlung ansprechen.
39. Dosierungsform nach Anspruch 38 zur Verwendung bei der Behandlung von Abstoßungsreaktionen durch Transplantation von Organen oder Geweben oder bei der Behandlung einer Autoimmunerkrankung.
40. Dosierungsform nach Anspruch 16 zur Verwendung bei der Behandlung eines Patienten, der dies benötigt, mit einer einmal täglichen Dosierung von Tacrolimus von 0,02 mg/kg/Tag bis 0,15 mg/kg/Tag.
41. Verfahren zur Herstellung der Zusammensetzung nach Anspruch 1, wobei das Verfahren den Schritt des Auflöses von Tacrolimus in Polyethylenglycol und Poloxamer zum Erhalten einer festen Lösung bei Umgebungstemperatur umfasst.

Revendications

1. Composition pharmaceutique comprenant une solution solide de tacrolimus dissous dans un véhicule hydrophile ou miscible à l'eau, dans laquelle le véhicule est un mélange de polyéthylèneglycol et de poloxamère dans une proportion comprise entre 1:3 et 10:1, où le point de fusion du véhicule est d'au moins 20 °C et où le tacrolimus est contenu à une concentration comprise entre environ 0,01 % p/p et environ 15 % p/p pour former une solution solide à température ambiante.
2. Composition selon la revendication 1, dans laquelle la concentration de tacrolimus dans le polyéthylèneglycol et le poloxamère est au plus de 10 % p/p.
3. Composition selon la revendication 1, dans laquelle la concentration de tacrolimus dans le polyéthylèneglycol et le poloxamère est au moins d'environ 0,05 % p/p.
4. Composition pharmaceutique selon la revendication 1, dans laquelle au moins 50 % p/p de tacrolimus est libéré en moins de 30 minutes environ, lors de n'importe quel test de dissolution effectué conformément à la Pharmacopée des Etats-Unis en utilisant un milieu de dissolution aqueux.
5. Composition pharmaceutique selon la revendication 1, dans laquelle au moins 75 % p/p de tacrolimus est libéré en moins de 40 minutes environ, lors de n'importe quel test de dissolution effectué conformément à la Pharmacopée des Etats-Unis en utilisant un milieu de dissolution aqueux.
6. Composition pharmaceutique selon la revendication 1, dans laquelle au moins 90 % p/p de tacrolimus est libéré en moins de 60 minutes environ, lors de n'importe quel test de dissolution effectué conformément à la Pharmacopée des Etats-Unis en utilisant un milieu de dissolution aqueux.
7. Composition pharmaceutique selon la revendication 1, dans laquelle le polyéthylèneglycol a un poids moléculaire moyen d'au moins 1500.
8. Composition pharmaceutique selon la revendication 1, dans laquelle le polyéthylèneglycol et le poloxamère sont présents dans une proportion comprise entre 1:1 et 5:1, de préférence entre 3:2 et 4:1, mieux encore entre 2:1 et 3:1, en particulier d'environ 7:3.
9. Composition pharmaceutique selon la revendication 1, dans laquelle le poloxamère est le poloxamère 188.
10. Composition pharmaceutique selon la revendication 1, dans laquelle le polyéthylèneglycol a un poids moléculaire moyen d'environ 6000 (PEG 6000).
11. Composition pharmaceutique selon l'une quelconque des revendications 1 à 10 comprenant en outre un ou plusieurs excipients pharmaceutiquement acceptables.
12. Composition pharmaceutique selon la revendication 11, dans laquelle les excipients pharmaceutiquement acceptables sont choisis dans le groupe constitué des agents diluants, désintégrant, liants et lubrifiants.

13. Composition pharmaceutique selon la revendication 11 se présentant sous une forme particulière, par exemple sous forme de poudre.
- 5 14. Composition pharmaceutique selon la revendication 13, dans laquelle les particules ont un diamètre moyen en poids géométrique, d_{gw} , d'environ 10 μm à environ 2000 μm , de préférence d'environ 20 μm à environ 2000 μm , et notamment d'environ 50 μm à environ 300 μm .
- 10 15. Composition pharmaceutique selon la revendication 13, dans laquelle les particules ont un diamètre moyen en poids géométrique, d_{gw} , d'environ 50 μm à environ 300 μm .
16. Forme galénique comprenant la composition pharmaceutique selon la revendication 11, qui est une forme galénique orale solide.
- 15 17. Forme galénique selon la revendication 16, qui est une forme galénique unitaire.
18. Forme galénique selon la revendication 16, qui comprend en outre un additif pharmaceutiquement acceptable choisi dans le groupe constitué des agents aromatisants, des agents colorants, des agents de masquage du goût, des agents de réglage du pH, des agents tampons, des conservateurs, des agents stabilisants, des antioxydants, des agents mouillants, des agents de réglage de l'humidité, des agents tensioactifs, des agents de mise en suspension, des agents améliorant l'absorption et des agents modifiant la libération.
- 20 19. Forme galénique selon la revendication 16, dans laquelle au moins un excipient pharmaceutiquement acceptable est choisi dans le groupe constitué de l'acide de silice ou d'un dérivé ou sel de celui-ci incluant les silicates, le dioxyde de silicium et leurs polymères ; l'aluminosilicate de magnésium et/ou l'aluminométasilicate de magnésium, la bentonite, le kaolin, le trisilicate de magnésium, la montmorillonite et/ou la saponite.
- 25 20. Forme galénique selon la revendication 16, dans laquelle au moins un excipient pharmaceutiquement acceptable est un acide de silice ou un dérivé ou sel de celui-ci.
- 30 21. Forme galénique selon la revendication 16, dans laquelle au moins un excipient pharmaceutiquement acceptable est le dioxyde de silicium ou un de ses polymères.
22. Forme galénique selon la revendication 18 comprenant un ou plusieurs agents modifiant la libération choisis dans le groupe constitué des polymères miscibles à l'eau, des polymères insolubles dans l'eau, des huiles et des matières huileuses.
- 35 23. Forme galénique selon la revendication 22, dans laquelle le polymère insoluble dans l'eau est choisi dans le groupe constitué de l'éthylcellulose, de l'acétate de cellulose, du nitrate de cellulose, et de leurs mélanges.
- 40 24. Forme galénique selon la revendication 22, dans laquelle l'huile ou la matière huileuse est choisie dans le groupe constitué des huiles ou matières huileuses hydrophiles et hydrophobes.
25. Forme galénique selon la revendication 22, dans laquelle l'huile ou la matière huileuse est hydrophile et choisie dans le groupe constitué des polyéthérglycols tels que les polypropylèneglycols ; des polyoxyéthylènes ; des polyoxypropylènes ; des poloxamères ; des glycérides polyglycolisés et de leurs mélanges.
- 45 26. Forme galénique selon la revendication 22, dans laquelle l'huile ou la matière huileuse est hydrophobe et choisie dans le groupe constitué des hydrocarbures saturés à chaîne droite, des esters de sorbitane, des paraffines ; des huiles et des graisses telles que le beurre de cacao, le suif de boeuf, le lard, les esters de polyéthers glycols ; d'un acide gras supérieur tel que l'acide stéarique, l'acide myristique, l'acide palmitique, des alcools supérieurs tels que le céanol, l'alcool stéarylique, des cires à bas point de fusion telles que le monostéarate de glycéryle, le monooléate de glycéryle, le suif hydrogéné, l'alcool myristylique, l'alcool stéarylique, les monoglycérides substitués et/ou non substitués, les diglycérides substitués et/ou non substitués, les triglycérides substitués et/ou non substitués, la cire d'abeille jaune, la cire d'abeille blanche, la cire de carnauba, la cire de ricin, la cire du Japon, les monoglycérides acétylés ; des polymères de NVP, des polymères de PVP, des polymères acryliques, et de leurs mélanges.
- 50 27. Forme galénique selon la revendication 26, dans laquelle l'huile ou la matière hydrophobe huileuse a un point de fusion d'au moins 20 °C environ.
- 55

28. Forme galénique selon la revendication 22, dans laquelle le polymère miscible à l'eau est un dérivé de cellulose choisi dans le groupe constitué de l'hydroxypropylméthylcellulose (HPMC), de l'hydroxypropylcellulose (HPC), de la méthylcellulose, de la carboxyméthylcellulose sodique, de l'hydroxyéthylcellulose, des poloxamères, des stéarates de polyoxyéthylène, de la poly-ε-caprolactone, de la polyvinylpyrrolidone (PVP), du copolymère de polyvinylpyrrolidone-poly(acétate de vinyle) PVP-PVA, des polymères polyméthacryliques et de l'alcool polyvinylique (PVA), du poly(oxyde d'éthylène) (PEO) et de leurs mélanges.
29. Forme galénique selon la revendication 22, qui est revêtue d'un enrobage gastro-résistant au moyen d'un polymère miscible à l'eau ayant une solubilité dans l'eau qui dépend du pH.
30. Forme galénique selon la revendication 29, dans laquelle le polymère miscible à l'eau est choisi dans le groupe constitué des polyacrylamides ; des dérivés de phtalate tels que les phtalates acides de glucides parmi lesquels l'acétophtalate d'amylose, l'acétophtalate de cellulose, le téréphtalate d'acétate de cellulose, l'isophtalate d'acétate de cellulose, d'autres phtalates d'esters de cellulose, des phtalates d'éthers de cellulose, le phtalate d'hydroxypropylcellulose, l'acétophtalate d'hydroxypropylcellulose, le phtalate d'hydroxypropyléthylcellulose, le phtalate d'hydroxypropylméthylcellulose (HMPCP), le phtalate de méthylcellulose, l'acétophtalate de méthylcellulose, l'acétophtalate de polyvinyle, l'hydrogénophtalate de poly(acétate de vinyle), l'acétophtalate de cellulose sodique, le phtalate acide d'amidon ; des phtalates d'autres composés parmi lesquels l'acétophtalate de polyvinyle (PVAP) ; d'autres dérivés de cellulose parmi lesquels l'acétosuccinate d'hydroxypropylméthylcellulose (HPMCAS), la carboxyméthylcellulose, l'acétotrimellitate de cellulose ; des alginates ; des carbomères ; des dérivés d'acide polyacrylique tels que les copolymères d'acide acrylique et d'ester acrylique, l'acide polyméthacrylique et ses esters, les copolymères d'acide poly(acrylique/méthacrylique), les copolymères d'acide méthacrylique ; du copolymère de styrène-acide maléique/phtalate de dibutyle, du copolymère de styrène-acide maléique/acétophtalate de polyvinyle, des copolymères de styrène et d'acide maléique ; de la gomme-laque, du glycolate d'amidon ; de la polacryline ; des copolymères d'acétate de vinyle et d'acide crotonique, et de leurs mélanges.
31. Forme galénique selon la revendication 29, qui lors de son administration orale à un mammifère qui en a besoin, libère au plus environ 10 % p/p, de préférence au plus environ 7,5 % p/p, mieux encore au plus environ 5 % p/p, et notamment au plus environ 2 % p/p de la quantité totale de principe actif dans les 3 premières heures, de préférence en moins de 2 heures, mieux encore en moins d'une heure, et notamment en moins de 30 minutes environ après administration.
32. Forme galénique solide selon la revendication 16, dans laquelle la forme galénique solide lors de son administration orale à un mammifère qui en a besoin, libère au moins 50 % p/p du principe actif en moins de 24 heures, de préférence en moins de 20 heures, mieux encore en moins de 18 heures, notamment en moins de 15 heures, et en particulier en moins de 12 heures.
33. Utilisation de la composition selon la revendication 1 pour la préparation d'une forme galénique orale solide telle que comprimés, capsules ou sachets.
34. Utilisation de la composition selon la revendication 1 pour la préparation de granules, pastilles, microsphères ou nanoparticules.
35. Utilisation de la composition selon la revendication 1 pour la préparation d'une forme galénique solide à libération immédiate.
36. Utilisation de la composition selon la revendication 1 pour la préparation d'une forme galénique solide à libération retardée.
37. Utilisation de la composition selon la revendication 1 pour la préparation d'une forme galénique topique.
38. Forme galénique selon la revendication 16 destinée à être utilisée dans le traitement de pathologies qui répondent à un traitement par le tacrolimus.
39. Forme galénique selon la revendication 38 destinée à être utilisée dans le traitement de réactions de rejet suite à une greffe d'organes ou de tissus ou le traitement de maladies auto-immunes.
40. Forme galénique selon la revendication 16 destinée à être utilisée dans le traitement d'un patient qui en a besoin

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avec une posologie de 0,02 mg/kg/jour à 0,15 mg/kg/jour de tacrolimus en administration quotidienne unique.

41. Procédé de préparation de la composition selon la revendication 1, ledit procédé comprenant l'étape consistant à dissoudre le tacrolimus dans du polyéthylèneglycol et un poloxamère pour obtenir une solution solide à température ambiante.

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REFERENCES CITED IN THE DESCRIPTION

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